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NASA'S BIOMEDICAL RESEARCH PROGRAM

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NASA'S BIOMEDICAL RESEARCH PROGRAM

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NASA'S BIOMEDICAL RESEARCH PROGRAM

By Chung-Hae Ahn

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FOREWORD

The biomedical research program has been established to investigate the major physiological and psychological problems encountered by man when he undertakes spaceflight. The program seeks to obtain a better definition of each problem, an understanding of its underlying mechanism, and ultimately a means of prevention. In pursuing these goals the program also includes a major effort to develop the research tools and procedures it needs where these are not being developed elsewhere.

After almost twenty years of manned spaceflight activities and after a much longer period of space related ground-based research, the program now recognizes two characteristics of spaceflight which are truly unique to space. These are weightlessness itself and one specific form of radiation. Although other environmental factors are clearly entailed, none so clearly limits man's ability to endure prolonged spaceflight. In its present stage of maturity much of the research focuses on mechanisms underlying the basic responses of man and animals to weightlessness.

The program consists of nine elements or RTOPs (Research and Technology Operating Plans). Eight of these RTOPs are referable to specific physiological problems that have either been encountered in previous manned spaceflight or which are anticipated to occur as spaceflights last longer, traverse steeper orbital inclinations, or are otherwise different from previous missions. The ninth RTOP addresses problems that have neither arisen nor can be reasonably predicted but are suspected on the basis of theoretical models, ground-based animal research, or for other reasons.

The program's current emphasis is directed toward the motion sickness problem because of its relevance to Space Shuttle operations. Increased awareness and understanding of the radiation hazard has resulted in more emphasis being placed on the biological effects of high energy, high mass number particulate radiation and upon radiation protection. Cardiovascular and musculoskeletal studies are pursued in recognition of the considerable fundamental knowledge that must be acquired in these areas before effective countermeasures to the effects of repetitive or long-term flight can be devised. Major new avenues of research will deal with the psychological accompaniments of spaceflight and with mathematical modelling of physiological systems.

Research is conducted in both intramural and extramural laboratories. The intramural laboratories are primarily those at Ames Research Center and Johnson Space Center with some peripheral efforts underway at Langley Research Center, Kennedy Space Center, and Jet Propulsion Laboratory. Extramural work is pursued throughout the United States in university, non-NASA government, and occasionally industrial laboratories. All research is managed by a center-based RTOP manager who reports, in a programmatic sense, to the headquarters disciplinary chief.

All research undertaken within this program is, by definition, ground-based. However, many of the experiments now selected or being considered for flight were conceived and nurtured by this ground-based program. The program is intimately related not only to the flight program, but to the programs of space biology and operational medicine as well.

This publication describing the biomedical research program was prepared for NASA by Allen Corporation of America, Alexandria, Virginia, under contract no. NASW-3439.

PAUL C. RAMBAUT, Sc.D.
Manager, Biomedical Research
Program
National Aeronautics and
Space Administration

PREFACE

The biomedical research program currently entails 95 projects in nine fields of investigation. The goals, activities, achievements, and/or future plans of each project are described in this report. Thus, this publication, the first of its kind in NASA's Life Sciences Division, presents a concise technical overview of the current research program.

The principal investigator (PI) for each project was requested to revise and update an abstract of that project, written from previously obtained information. The dates on the upper right-hand corner of each page refer to the date of response; those descriptions dated January, June, or July 1980 were neither revised nor updated. Returned abstracts were further revised to include only the information essential for describing the technical aspects of projects, the major thrust of the descriptions being recent achievements.

The PI was also requested to submit pertinent graphic material and a list of recent, significant publications resulting from the effort. Unfortunately, some project descriptions lack graphic material. For the most part, this is due to the absence of a suitable illustration or photo. At most, three publications per project are included. These were selected on the basis of relevance and retrievability; publications either "submitted" or "in press" are therefore excluded.

I would like to acknowledge and thank Dr. Paul C. Rambaut for his invaluable and extensive editorial and technical assistance. I would also like to thank Martha Granda, Lucille Kurtz, and Clare Coulter for cheerfully typing and retyping the text.

CHUNG-HAE AHN
Senior Research Scientist
Allen Corporation of America

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1. CARDIOVASCULAR DECONDITIONING

UNIQUE PROJECT NUMBER (UPN)	PRINCIPAL INVESTIGATOR (PI)	SHORT TITLE
199-20-11-01	Bhagat	Limb Volume Measuring Systems
199-20-11-02	Johnson	Physiological Performance Laboratory
199-20-11-03	Abboud	Cardiopulmonary Baroreceptors
199-20-11-04	Mark	Microprocessor Physiological Instrumentation
199-20-11-05	Blomqvist	Cardiovascular Effects of Exercise
199-20-11-06	Eckberg	Carotid Baroreflex
199-20-11-15	Lacy	Radionuclide Imaging System
199-20-12-02	Meindl	Implantable Telemetry for Small Animals
199-20-12-03	Sandler	Cardiovascular Response to Simulated Flight
199-20-12-05	Philpott	Ultrastructural Effects of Deconditioning
199-20-12-06	Rositano	Noninvasive Ultrasonometry
199-20-12-07	Hines	Biotelemetry Systems
199-20-12-08	Knapp	Dynamic Accelerative Countermeasures
199-20-12-11	Stone	Deconditioning Mechanisms in Primates
199-20-12-12	Greenleaf	Metabolism and Acceleration Tolerance
199-20-12-15	Harrison	Cardiovascular Stress and Regional Flow
199-20-13-01	Alexander	Maintenance of Fitness
199-20-14-02	Back	Diseased Coronary Arteries Under Stress

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INTRODUCTION

Previous manned spaceflights provide valuable data describing some of the more overt symptoms of cardiovascular deconditioning. In flight, the distribution of intravascular fluids shifts toward the upper part of the body, causing the tissues of the head and neck to swell and the volume of blood handled by the heart to increase. The shift may result in an initial enlarging of the heart to accommodate the increased load, as supported by the observed tendency toward lower heart rates for many of the astronauts in flight. The decrease in calf-girth or leg volume may be due largely to this shift, particularly given the extremely rapid recovery in size.

Baroreceptors in the heart and neck, as well as other volume control mechanisms, may compensate for the apparent increase in volume and pressure in the upper regions of the body by triggering losses in blood plasma and in red cell mass. These losses are further complicated by changes in levels of blood electrolytes (Na, Cl, K) and vasoactive hormones which may cause the slight tendency toward abnormal rhythm and timing of heart beats in flight.

Returning to Earth reverses the process initiated by weightlessness. The heart beats faster in response to the need to maintain cardiac output. Heart size is decreased noticeably (probably due to blood volume loss), and its electrical and mechanical activities indicate depressed function, e.g., a lower filling volume. Certain individuals display a greater tendency to arrhythmias.

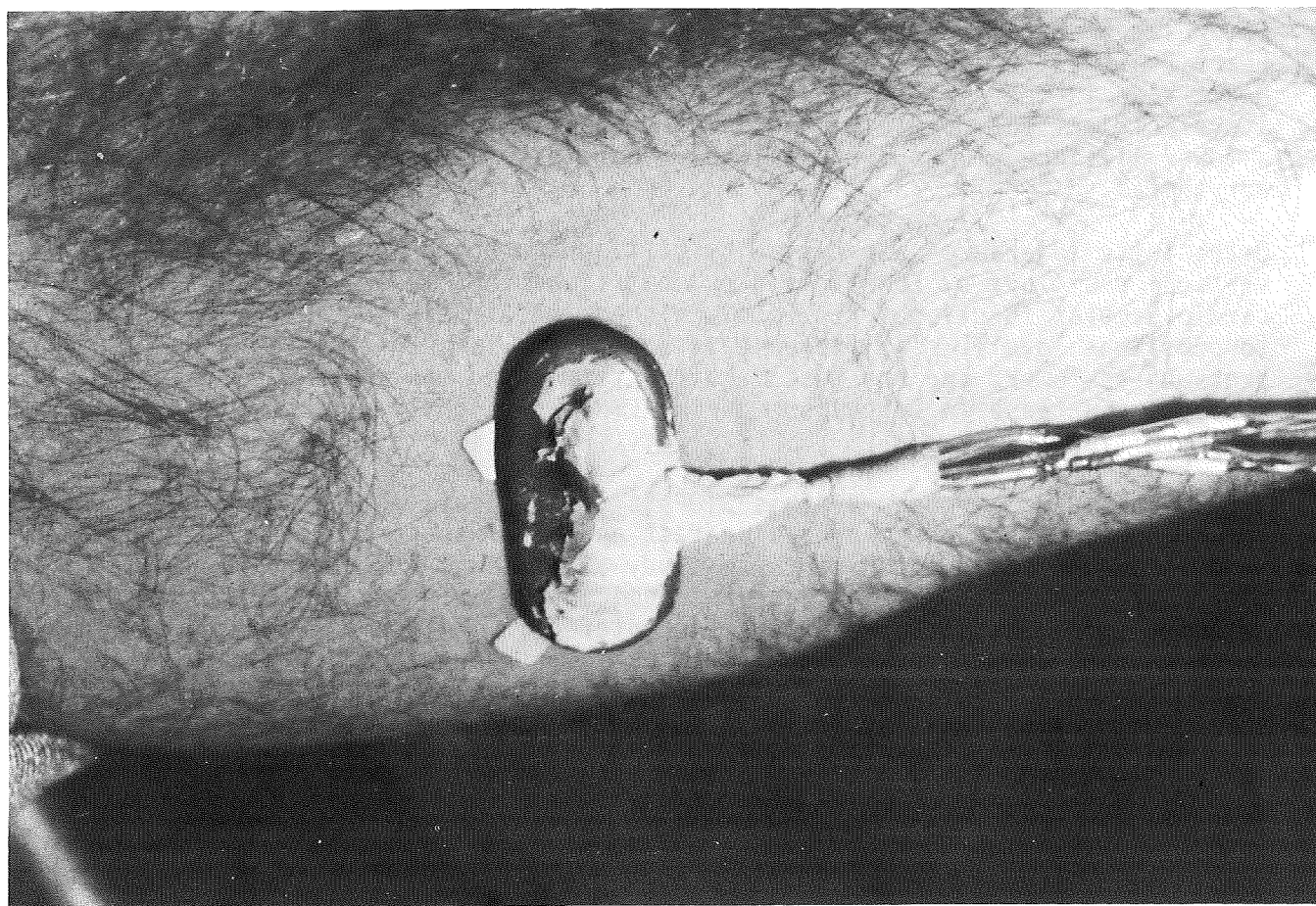
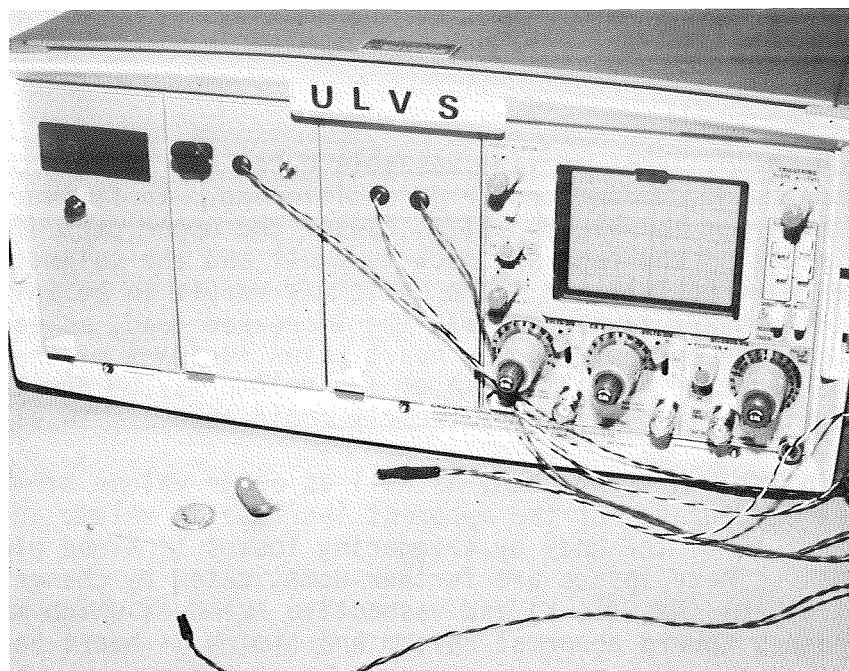
Orthostatic tolerance*, as tested by tilting the prone astronaut toward a vertical position, by LBNP**, and by centrifugation, is an indicator of cardiovascular functions. It is diminished immediately postflight, compared to preflight levels. The increase in heart rate is much greater; blood pressure is lower; and the test is often terminated early because of impending syncope. Increase in leg volume during LBNP is slightly greater postflight than preflight.

One of the major purposes of this RTOP is to elucidate the causal mechanisms for all these observed changes. Bedrest and other space analogs are being used in ground-based experiments to study alterations in cardiac response, blood volume and composition, and autonomic neural response in humans and in animal models. Technical barriers encountered in the process are addressed, whether it be in measuring the changes or in inducing them. Ultimately, procedures and/or devices for preventing or minimizing any impedance to full functional capacity of future space travelers will be developed. Current efforts toward these ends are described in the pages that follow.

*Orthostatic tolerance is the ability to stand and function in an upright position: adapted mechanisms and anatomic structures counter the hydrostatic forces of gravity on the cardiovascular system, thus preventing the pooling of fluids to the lower extremities, which would induce syncope (or fainting).

**The application of lower body negative pressure (LBNP) shifts fluids back toward the legs in prone humans in much the same way as gravitational stress pulls down fluids in standing humans. In flight LBNP tests show a dramatic increase in leg volume and a decrease in orthostatic tolerance similar to the changes observed immediately postflight. The increase in leg volume immediately postflight is not as dramatic as when induced by LBNP in flight, but the decrease in orthostatic tolerance immediately postflight is quite comparable to that induced by LBNP in flight.

Bhagat
11-01



Ultrasonic Limb Volume System (ULVS). Top: Display and computer are shown with transmitting and receiving crystals. Bottom: These transducers are attached to the mid-calf section of the leg.

199-20-11-01

AUG 1980

FEASIBILITY AND EVALUATION STUDY OF LIMB VOLUME MEASURING SYSTEMS

P. K. Bhagat (University of Kentucky College of Engineering)

Research in the biomedical field involves a continual quest for better measurement devices. An ultrasonic plethysmograph has been developed with the need for a better assessment of limb diameter in mind. This ultrasonic system uses a microprocessor which computes the cross-sectional area from two chord lengths that are measured independently. The concept of using ultrasound was an outgrowth of the successful development of an instrument for measuring left ventricular volume.

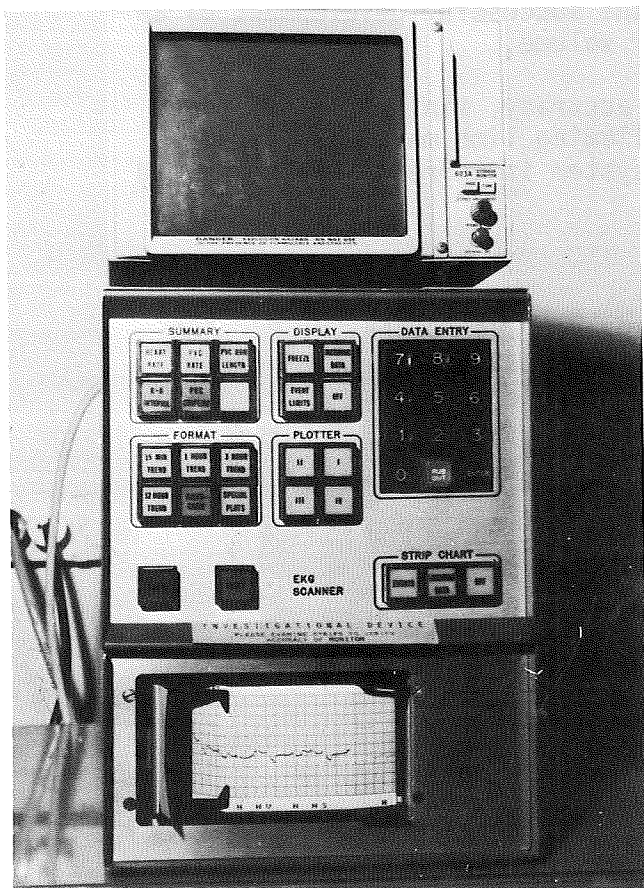
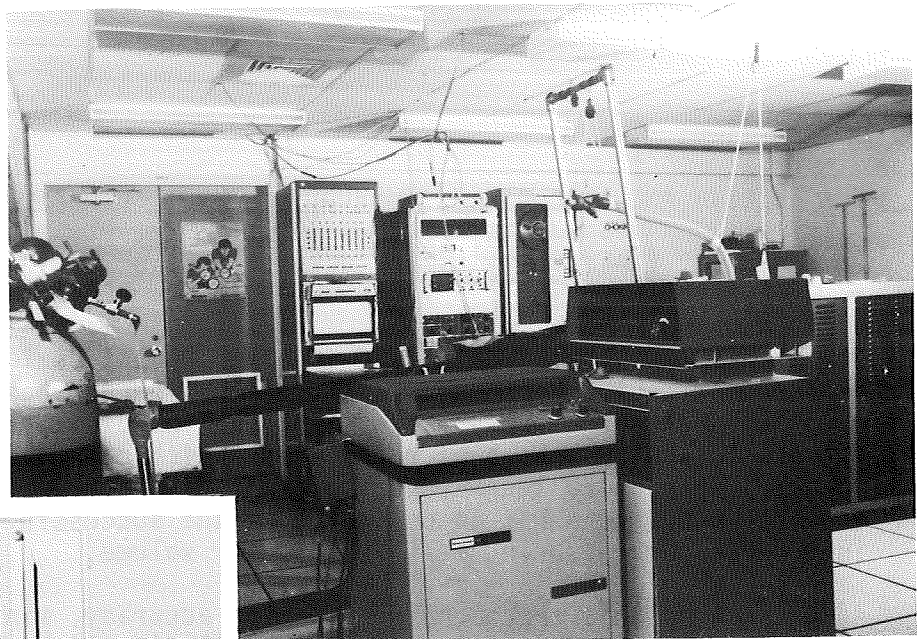
Advantages of this approach include high accuracy, minimal interference to the subject (being nonintrusive and allowing limb movement), ease of calibration and simplicity of use. The system is currently being tested for use in a flight experiment.

PUBLICATIONS

1. Bhagat, P. K., Lafferty, J. F., Bowman, D., and Kadaba, M. P. "An ultrasonic plethysmograph for spaceflight applications." AVIAT SPACE ENVIRON MED 51(2):185-188, 1980.

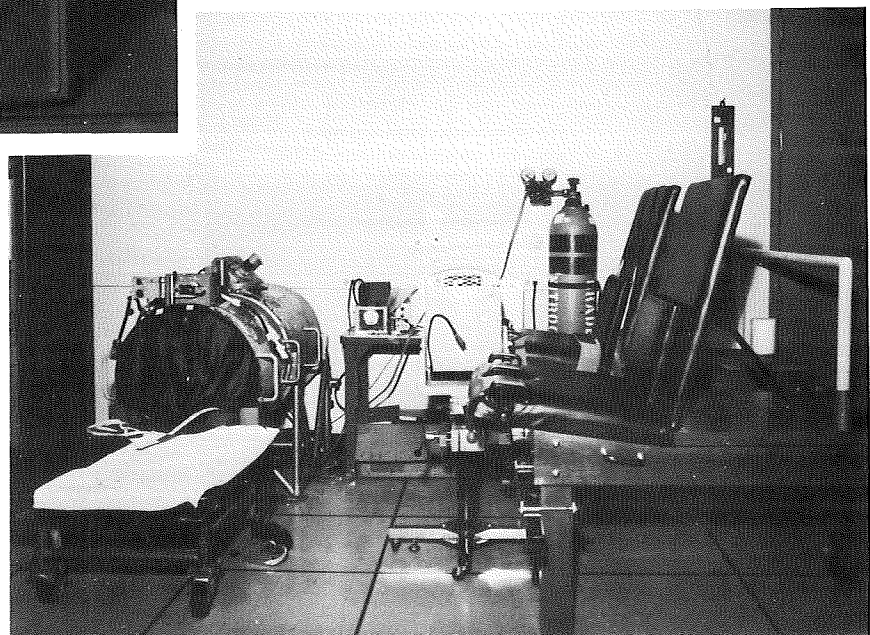
Johnson
11-02

Cardio-Performance
Laboratory
(panoramic view).



NASA-Developed Arrhythmia
Monitor for bedside use.

Lower Body Negative
Pressure (LBNP):
Potential cardiovas-
cular countermeasure
in Shuttle flights.



199-20-11-02

SEP 1980

IN-HOUSE SUPPORT OF NASA-JSC PHYSIOLOGICAL PERFORMANCE LABORATORY

P. C. Johnson (NASA-JSC)

The JSC Physiological Performance Laboratory performs research tasks that contribute to an understanding of the human cardiovascular system and associated physiological systems (e.g., lungs, central nervous system, kidneys) that may be affected by circulatory stresses during spaceflight. Astronauts and astronaut candidates are tested for cardiac and pulmonary performance, as well as for fat-to-muscle-mass relationships. Marathon runners are tested for comparison with returned astronauts.

In addition to providing research support, the laboratory also tests systems to be used in flight experiments. Laboratory studies include the use of LBNP, bicycle, treadmill ergometry, and other pertinent stress procedures. Emphasis is placed on the development and verification of noninvasive and minimally invasive techniques.

A device currently being tested is useful in coronary care units or in mission control. It automatically records, stores, and analyzes aberrant heart cycles. By providing a nearly automatic way to analyze and alert the mission surgeon of potentially dangerous cycles, it eliminates the need for constant visual surveillance.

Also being tested is an ultrasound device which accurately measures diameter changes and will be used to measure crewmembers' calf sizes both in flight and postflight. These measurements will facilitate the localization and understanding of in-flight fluid shifts.

PUBLICATIONS

None

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199-20-11-03

AUG 1980

NEUROCIRCULATORY CONTROL MECHANISMS: ROLE OF CARDIOPULMONARY BARORECEPTORS

F. M. Abboud (University of Iowa College of Medicine)

The purpose of this project is to examine the role of cardiopulmonary baroreceptors in renal control in humans. Such neurocirculatory control mechanisms may be deranged in space and upon return to Earth.

Studies in humans revealed that the cardiopulmonary baroreceptors exert a major influence on forearm vascular resistance, while the carotid baroreceptors greatly affect the splanchnic vasoconstriction response and quickened heart rate observed during venous pooling.

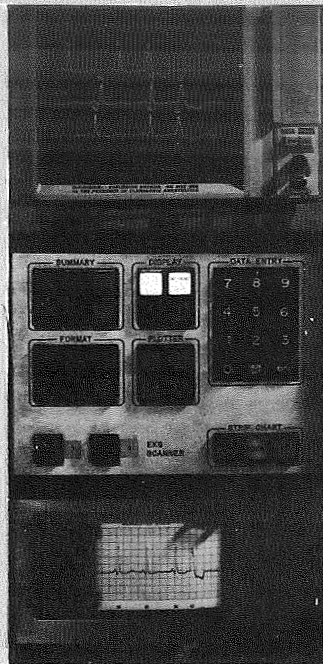
Cardiopulmonary baroreceptor activity affects renal sodium secretion without affecting renal blood flow, glomerular filtration rate, aldosterone, and antidiuretic hormone.

The effects of venous pooling (induced by LBNP for 30 minutes at 20mmHg) have been compared with those of increased venous return (induced by leg elevation). The results are being analyzed currently.

PUBLICATIONS

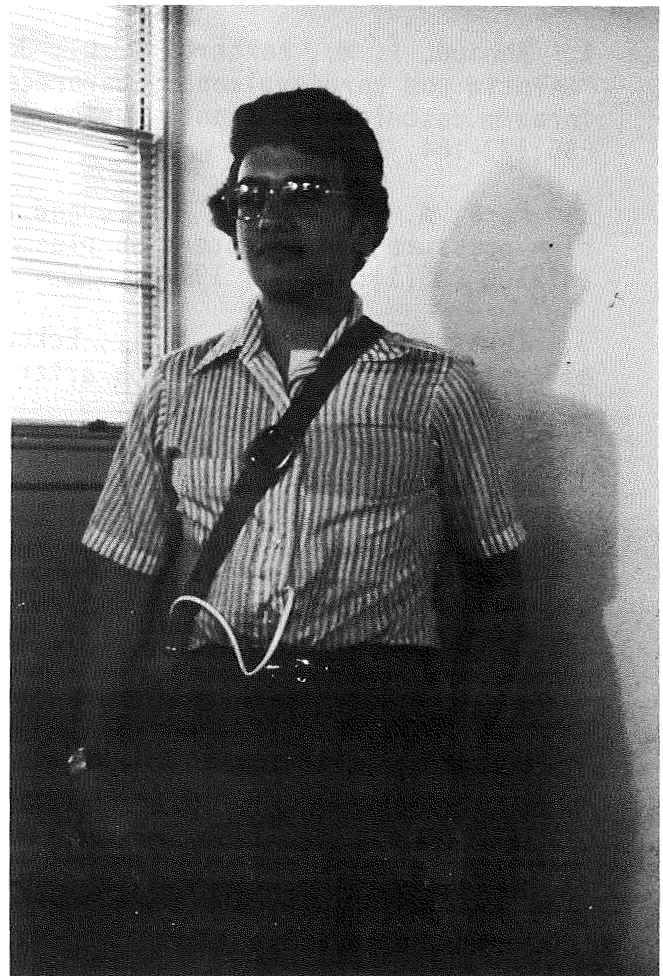
1. Abboud, F. M., Eckberg, D. L., Johannsen, U. J., and Mark, A. L. "Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man." J PHYSIOL 286:173-184, 1979.
2. Mark, A. L., Abboud, F. M., and Fitz, A. E. "Influence of low- and high-pressure baroreceptors on plasma renin activity in humans." AM J PHYSIOL 235(1):H29-33, 1978.
3. Takeshita, A., Mark, A. L., Eckberg, D. L., and Abboud, F. M. "Effect of central nervous pressure on arterial baroreflex control of heart rate." AM J PHYSIOL 236:H42-47, 1979.

Mark
11-04



Left: Single-Patient Arrhythmia Analysis System. This computer detects and categorizes each heartbeat as it occurs, displaying it on the accompanying storage oscilloscope. The screen may also display statistical analysis and trends, along with the criterion for current detection. Graded alarms are also incorporated.

Right: Portable Arrhythmia Analysis Computer. The complete computer is inside a leather bag hanging by the volunteer's right side. Three electrodes are affixed to his chest and are attached to the computer by a cable. The computer is powered by batteries which are adequate for 24 hrs at a time. It weighs less than 4 lbs and provides a beat-by-beat analysis of the patient's electrocardiograms.



199-20-11-04

OCT 1980

MICROPROCESSOR-BASED PHYSIOLOGICAL INSTRUMENTATION

R. G. Mark (Beth Israel Hospital)

Initial work concentrated on a patient-carried portable computer powered by batteries adequate for at least 24 hours. The system detects and categorizes each heartbeat and analyzes the cardiac rhythm, summarizing it both statistically and in terms of specific events. The portable system is supported by and communicates with a hospital base station.

More recently, efforts have been on a single patient bedside arrhythmia monitor which includes operational controls, displays, and hard-copy output. This system provides statistical summaries as well as monitors the output.

PUBLICATIONS

None



Bedrest subject undergoing physiological tests. Subject is being tested for tolerance to LBNP after -50° head-down bedrest. Note the black cover of the LBNP machine encasing the man's waist.

CARDIOVASCULAR EFFECTS OF VARIATIONS IN HABITUAL LEVELS OF PHYSICAL ACTIVITY

C. G. Blomqvist (University of Texas Southwestern Medical School)

Bedrest studies (24-hour, -5° head-down) do not provide evidence that the heart will be chronically overloaded under these conditions. Central venous pressure increases within 90 minutes but then decreases to below resting levels by the end of 24 hours; the left ventricular diameter reacts oppositely, initially decreasing, then increasing. There are no effects of bedrest on heart muscle function.

Future studies will explore the mechanism of changes involved, as well as the effect of age on adaptation. A comparison of athletes' and non-athletes' responses will be made. Surface body cooling will be tested as a counter-measure; preliminary results are encouraging.

PUBLICATIONS

1. Nixon, J. V., et al. "Early cardiovascular adaptation to simulated zero gravity." J APPL PHYSIOL 46(3):541-48, 1979.
2. Blomqvist, C. G., et al. "Early cardiovascular adaptation to zero gravity stimulated by head-down tilt." ACTA ASTRONAUT 7(4-5):543-554, 1980.
3. Raven, P. B., et al. "Interactions between surface cooling and LBNP-induced central hypovolemia." AVIAT SPACE ENVIRON MED 51(5):497-503, 1980.



Subject wearing neck collar that applies precise pressure changes.

CAROTID ARTERIAL BAROREFLEX MECHANISMS IN MAN

D. L. Eckberg (Veterans Administration Medical Center)

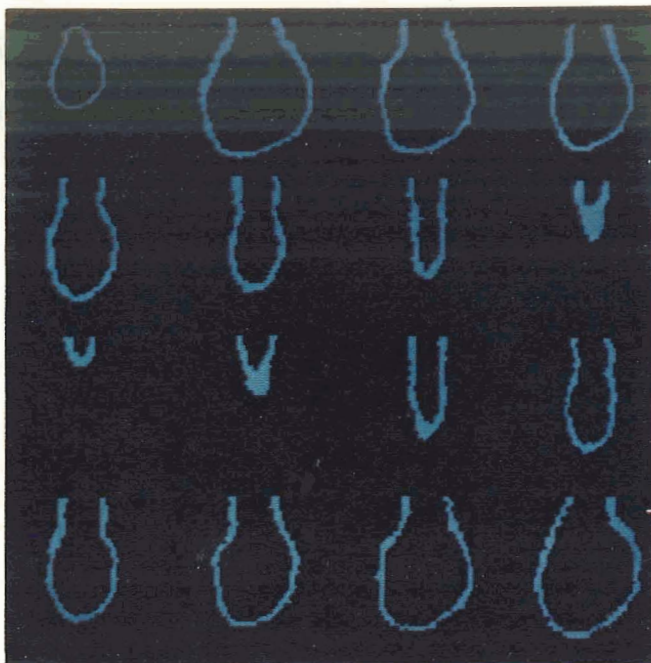
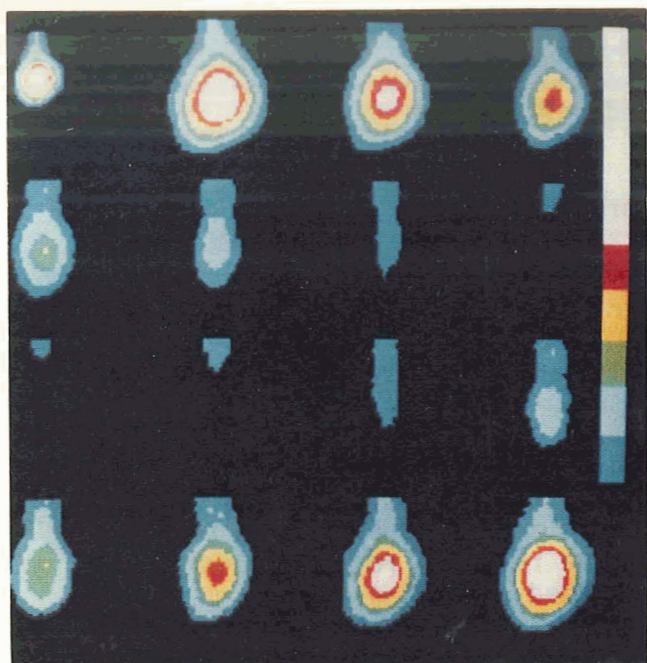
A neck collar has been devised to apply precise changes of pressure to the carotid sinus nodes. Altered stretch of these arteries affects the neural messages sent from the nodes to the vasomotor center and the cardioinhibitory center in the brain. These centers then act to modify the heart rate and diameter of blood vessels in order to maintain a normal blood pressure at all times. Thus, distention of the arterial walls due to rise in pressure will inhibit vasoconstriction and excite cardioinhibition.

It is possible that the substantial headward shift of vascular fluids induced by weightlessness during spaceflight impairs this normal cardiovascular reflex control mechanism. Such impairment is indicated by a fall in blood pressure upon standing in astronauts who have recently returned from spaceflight. Neck pressure or suction has been used experimentally to perturb this reflex mechanism in order to understand how this system works under normal and abnormal circumstances. The entire stimulus-response reflex has been defined in man as a result of this effort (see reference 3).

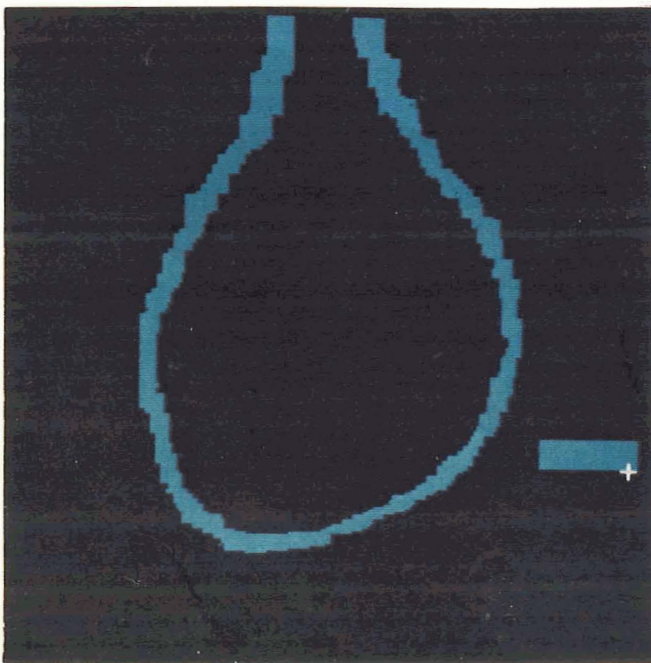
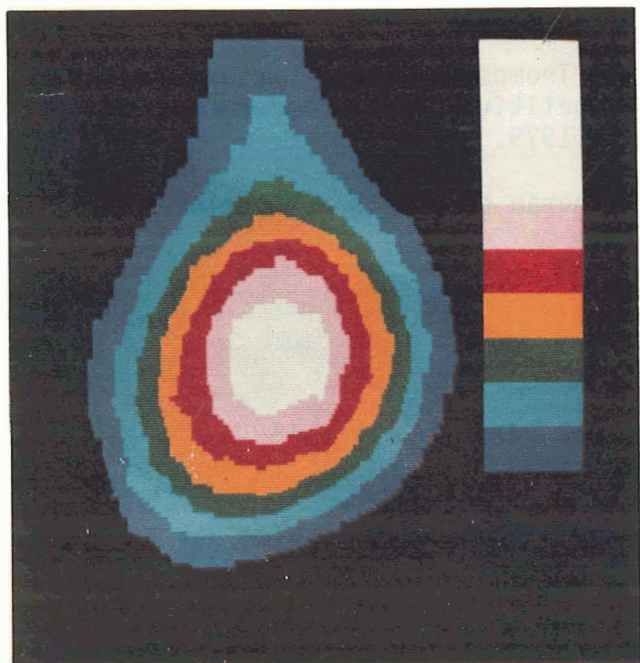
Subsequent and future efforts attempt to understand how the central nervous system controls the caliber of blood vessels. For this research, traffic over nerves destined for blood vessels will be measured directly in alert, cooperating volunteers with microneedles inserted almost painlessly through the skin into nerve bundles.

PUBLICATIONS

1. Eckberg, D. L. "Carotid baroreflex function in young men with borderline blood pressure elevation." CIRC 59:632-636, 1979.
2. Baskerville, A. L., Eckberg, D. L., and Thompson, M. A. "Arterial pressure and pulse interval responses to repetitive carotid baroreceptor stimuli in man." PHYSIOL (Lond) 297:61-71, 1979.
3. Eckberg, D. L. "Nonlinearities of the human carotid baroreceptor-cardiac reflex." CIRC RES 47:208-216, 1980.



Imaging application of multiwire proportional counter. Above: Sixteen stop-action views of the phantom heart and its wall-perimeter images through one cycle of contraction and expansion (left to right, top to bottom). Below: Phantom image and wall-perimeter images at diastole (140 ml volume).



FABRICATION OF RADIATION DETECTION AND QUANTITATION SYSTEM

J. L. Lacy (NASA-JSC)

The purpose of this project is to develop and to test a radionuclide imaging system for monitoring cardiac function in flight. Multiwire proportional counter (MPC) technology has been adapted for this project.

This laboratory has developed a sophisticated yet simple technique for electronic readout of the MPC, which detects ionizing radiation. The system is tested on a cardiac phantom, which consists of a fluid-filled rubber bag with a volume that can be rapidly modulated to simulate the human left ventricle. A radioactive tracer is viewed with the MPC imaging device. Using the phantom, one can determine stroke profile, ejection fraction, and pulse rates.

Recently, the production of a continuous supply of the short half-life isotope tantalum-178 ($T_{1/2} = 9.3$ min) has been possible. This development makes the use of this system more practical and safe, opening new areas of diagnostic and other research capabilities.

PUBLICATIONS

None

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IMPLANTABLE TELEMETRY FOR SMALL ANIMALS

J. Meindl (Stanford Electronics Laboratory)

Hemodynamic flight experiments using small animals call for a reduction in size of implanted instrumentation while improving reliability; this can be achieved by sophisticated electronic systems that use advanced integrated circuitry. Integrated circuit design is being applied to the development of pressure, flow, and dimension measurement systems to assess blood flow changes in kidneys, heart, and head.

Doppler ultrasonic flow systems seem to provide the most reasonable option. Improved CW* Doppler ultrasonic systems suitable for use in small primates have been developed and are now being tested for use in LBNP and acceleration tests. The system is battery operated, completely implantable, and can send data over distances of at least 50 feet. In addition, systems that make pressure and dimension measurements simultaneously are being developed.

An experiment utilizing these concepts has been accepted for experiment definition aboard the Space Shuttle. Single channel Doppler systems will be implanted in at least six monkeys to measure flow in the ascending aorta and in a renal vessel. Current capabilities and concepts will be expanded and refined to better suit spaceflight requirements.

PUBLICATIONS

1. Claude, J. P., Griffin, J. R., Gschwend, S. J., Knutti, J. W., Allen, H. V., and Meindl, J. D. "A chronically instrumented animal model for electrophysiologic research." PROC IEEE BIOMED 26(9):545, 1979.
2. Knutti, J. W., Allen, H. V., and Meindl, J. D. "Integrated circuit implantable systems." BIOMED SCI INST 15:105-107, 1979.
3. Sander, C. S., Knutti, J. W., and Meindl, J. D. "A monolithic capacitive pressure sensor with pulse-period output." IEEE International Solid-State Circuits Conference, Digest of Technical Papers, 1980.

*Continuous waves

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199-20-12-03

JUL 1980

CARDIOVASCULAR RESPONSE TO SIMULATED SPACEFLIGHT STRESS

H. Sandler (NASA-ARC)

Horizontally body-cased animals (7, 14 & 30 days, respectively) have been evaluated by LBNP and +G_z using chronically implanted instrumentation. Animal response was similar to human response during bedrest.

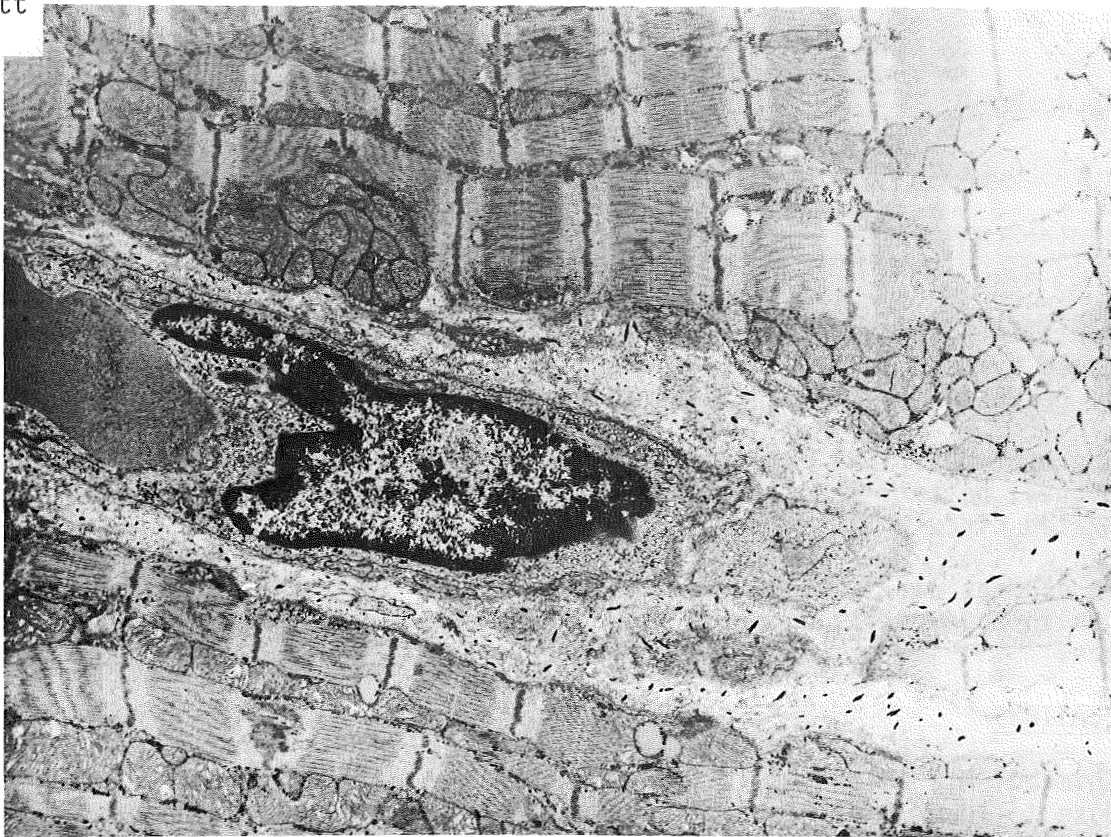
These prototype flight experiments involved use of conventional hardware techniques, battery-less telemetry units, and advanced battery-powered integrated circuit units.

Future studies will involve long term (1-2 mos.) monitoring of animals, changes in body position, blood flow distribution, and heart function changes.

PUBLICATIONS

1. Shimizu, M., Ghista, D. N., and Sandler, H. "Cardiovascular regulatory response to lower body negative pressure following blood volume loss." AVIAT SPACE ENVIRON MED 50:24-25, 1979.
2. Dickey, D. T., Teoh, K. K., Sandler, H., and Stone, H. L. "Changes in blood volume and response to vasoactive drugs in horizontally cased primates." PHYSIOLOGIST 22(6):S-27, 1979.
3. Sandler, H. "Low-G stimulation in mammalian research." PHYSIOLOGIST 22(6):S-19, 1979.

Philpott
12-05



Ultrastructural effects of cardiovascular deconditioning. Top: A capillary with an endothelial cell is seen along with normal myocardial structure from a rhesus monkey (X14,000). Bottom: Rhesus monkey was body-casted for 35 days. Beside the proliferation of connective tissue, a white blood cell (large arrow) and a fragment of macrophage (small arrow) are seen (X10,000).

199-20-12-05

SEP 1980

CELLULAR CONSEQUENCES AND ULTRASTRUCTURAL EFFECTS OF CARDIOVASCULAR DECONDITIONING

D. E. Philpott (NASA-ARC)

Morphological alterations induced by hypokinesia and altered gravitational forces are studied at the cellular and subcellular level. Mechanisms responsible for cardiovascular deconditioning are also under investigation.

Model systems use restricted activity, greater gravitational forces, or a combination of both to simulate reentry forces. Hearts from rats exposed to varying levels of chronic acceleration (2.3 and 4.1G) exhibit gross microscopic and ultrastructural changes, including changes in the size of fibers, the number of mitochondria, and in protein synthesis. Restricted activity or bedrest results in a decrease in mitochondrial volume.

Further investigations of chaired and horizontally body-casted monkeys will continue and should produce quantifiable data on other changes.

PUBLICATIONS

1. Kato, K., Boloun, A., and Philpott, D. E. "Effect of supergravity on the areas of lipid droplets and mitochondria in the heart left ventricle." J ULTRASTRUCT RES 69(1):360, 1979.

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199-20-12-06

JUL 1980

NONINVASIVE ULTRASONOMETRY FOR MEASUREMENT OF CARDIOVASCULAR DYNAMICS

S. Rositano (NASA-ARC)

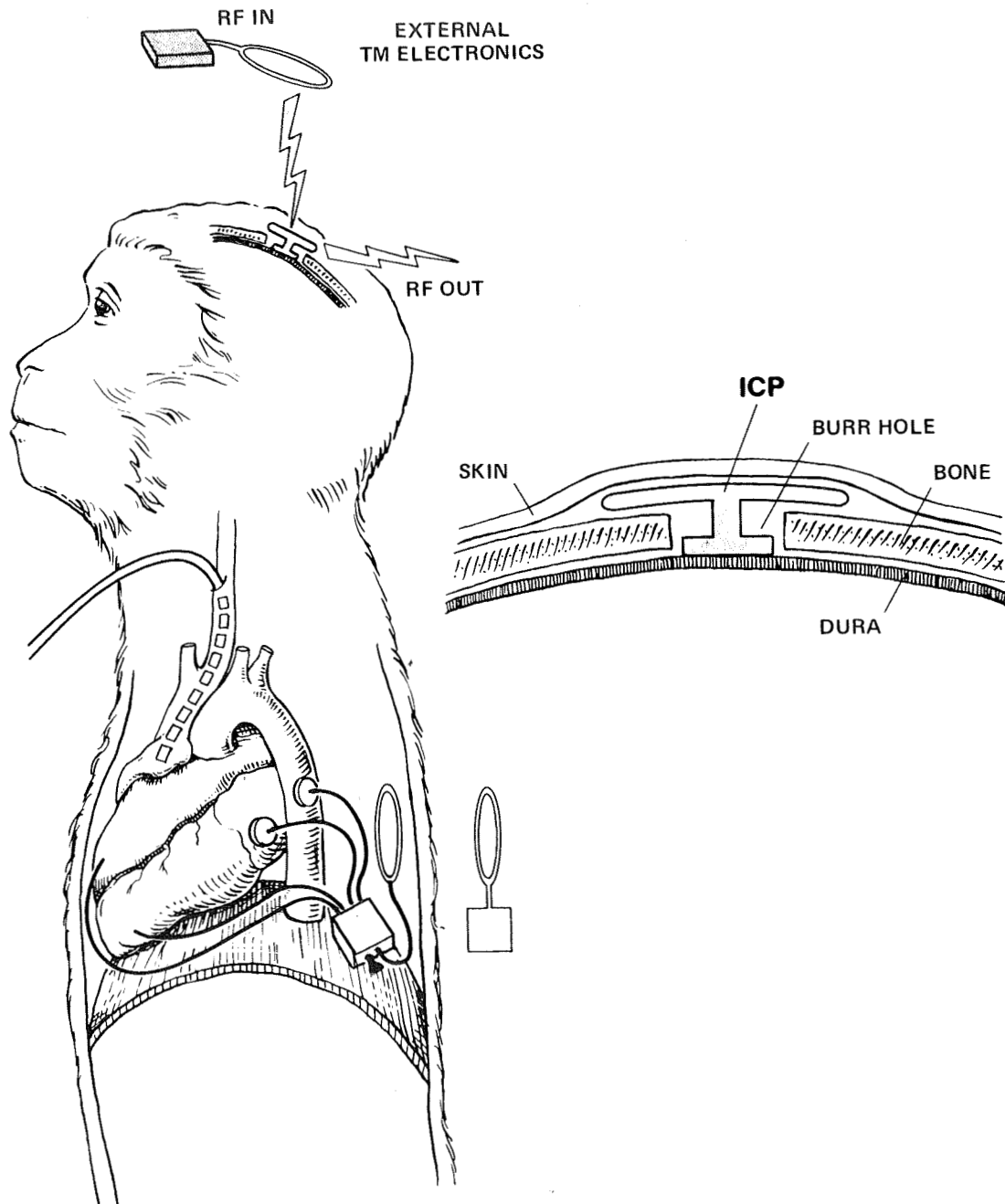
Techniques for measuring blood pressure and flow, which will determine acceleration ending points (being modified for use in Space Shuttle flights) have been developed.

A carotid pressure flow transducer for use in Kosmos 1981 experiment has also been developed.

Future work will involve continued work on microprocessor-based blood pressure (cuff) system; improving accuracy and reproducibility of Doppler flow signals; and development of pressure flow system, including calibration system.

PUBLICATIONS

None



Biotelemetry systems. Currently available biotelemetry systems were adapted for chronic implantation in rhesus monkeys. Here, systems for measuring intracranial pressure (ICP) and cardiovascular changes are shown.

BIOTELEMETRY SYSTEMS FOR CARDIOVASCULAR FLIGHT EXPERIMENTS

J. Hines and H. Sandler (NASA-ARC)

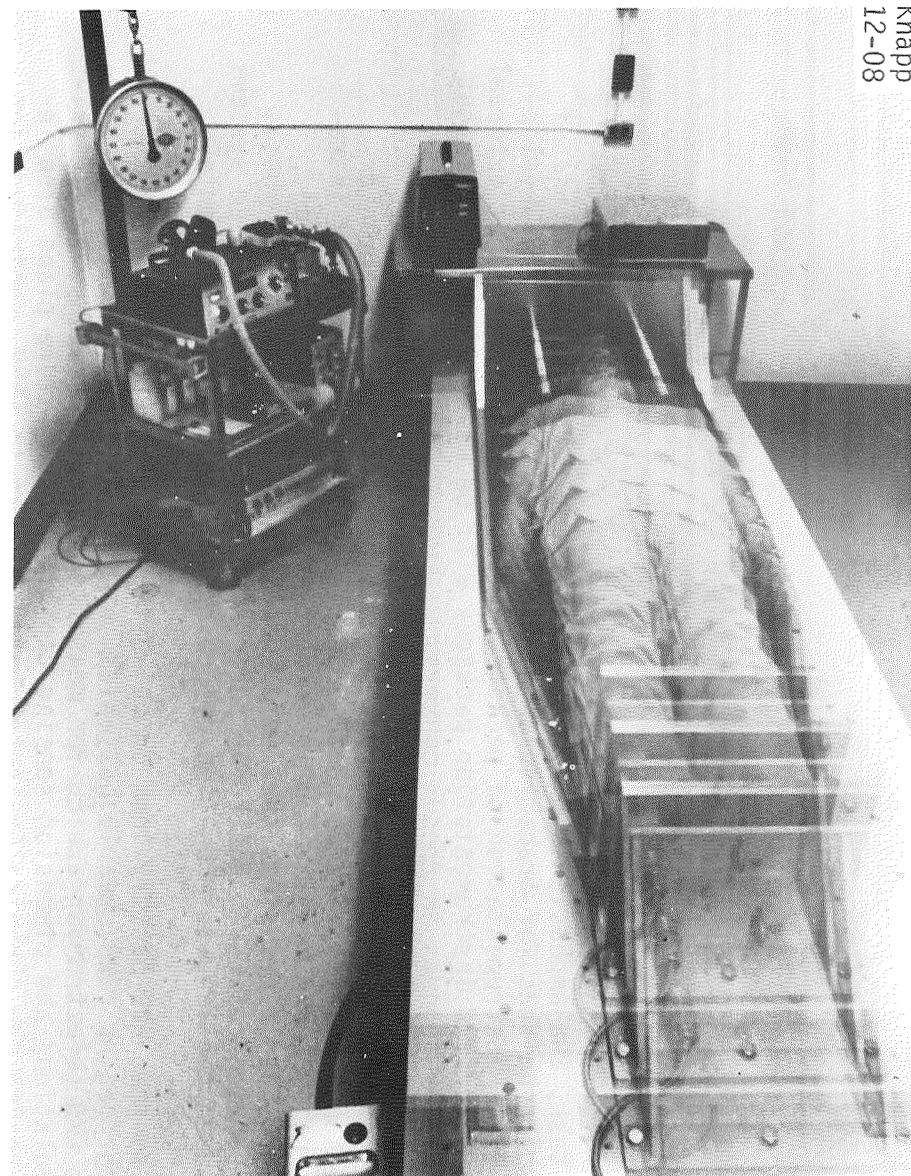
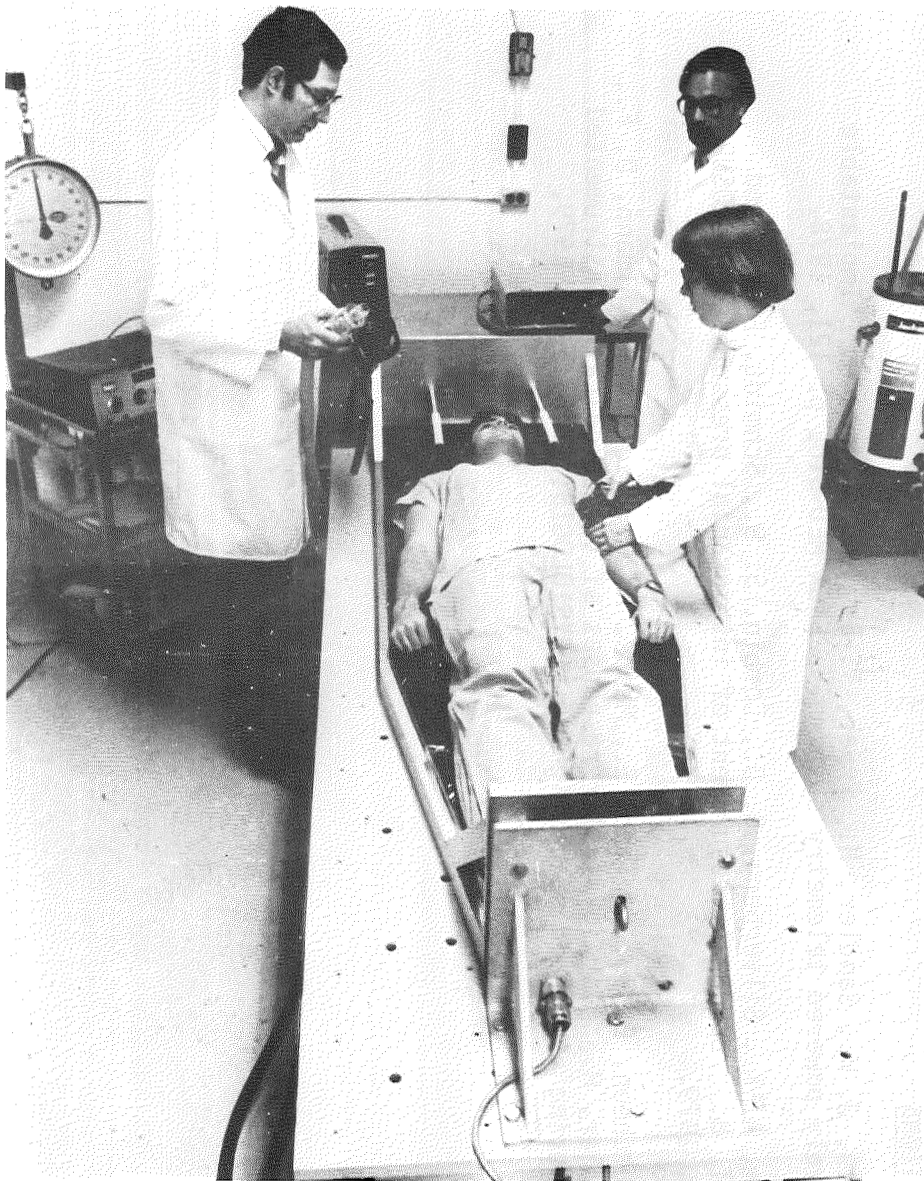
In this task, the emphasis is placed on transducer development, the use of telemetry techniques for transmission of biologic information, and development of small instrumentation of packages compatible for internal or external use. Miniaturized instrumentation packages will be used to monitor inflight cardiovascular changes in rhesus monkeys.

Currently available biotelemetry systems have been adapted for chronic implantation in small primates, with emphasis on the measurement of intracranial pressure and cardiovascular parameters. Multichannel pressure, temperature, and ECG systems that were successfully implanted in 20 rhesus monkeys provided usable signals for periods up to four months. These systems will be used for long-term on-line recording of data during experiments.

Present systems are battery-less or use batteries plus RF switches. Other work incorporates rechargeable batteries, as well as flow (electro-magnetic), ECG, and EMG (electromyographic, for measuring muscular response to electrical stimulation) and dimension sensing capabilities. Future plans also include exposing the chronically instrumented animals to LBNP, centrifugation, and restraint.

PUBLICATIONS

1. Hines, J. W., Sandler, H., Fryer, T. B., and Kojima, G. "Implantable inductively powered telemetry systems." ENGR MED BIOL p. 121, 1978.
2. Ream, A. K., Silverberg, G. D., Corbin, S. D., Schmidt, E. V., and Fryer, T. B. "Epidural measurement of intracranial pressure." NEUROSURG 5:36-43, 1979.
3. McCutcheon, E. P., Carlson, E., Mains, R. C., Pace, N., Rahlmann, D. F., and Sandler, H. "Cardiovascular responses of the chronically instrumented monkey during simulated spaceflight." PHYSIOLOGIST 22(6):5-55, 1979.



Knapp
12-08

Horizontal Whole-Body Oscillator. A subject is secured to the oscillator platform (left) and then oscillated at a set frequency and displacement (right).

DYNAMIC IMPOSED ACCELERATION FOR STRESS TESTING AND PREVENTION OF
CARDIOVASCULAR DECONDITIONING

C. F. Knapp (University of Kentucky)

Decreased stimulation of mechanoreceptors, particularly those related to peripheral vascular function, seems to have a significant role in the etiology of orthostatic intolerance upon return to Earth and after bedrest. Whole-body oscillatory acceleration may supply the necessary stimulation, along with weightless exercise, to be an effective countermeasure.

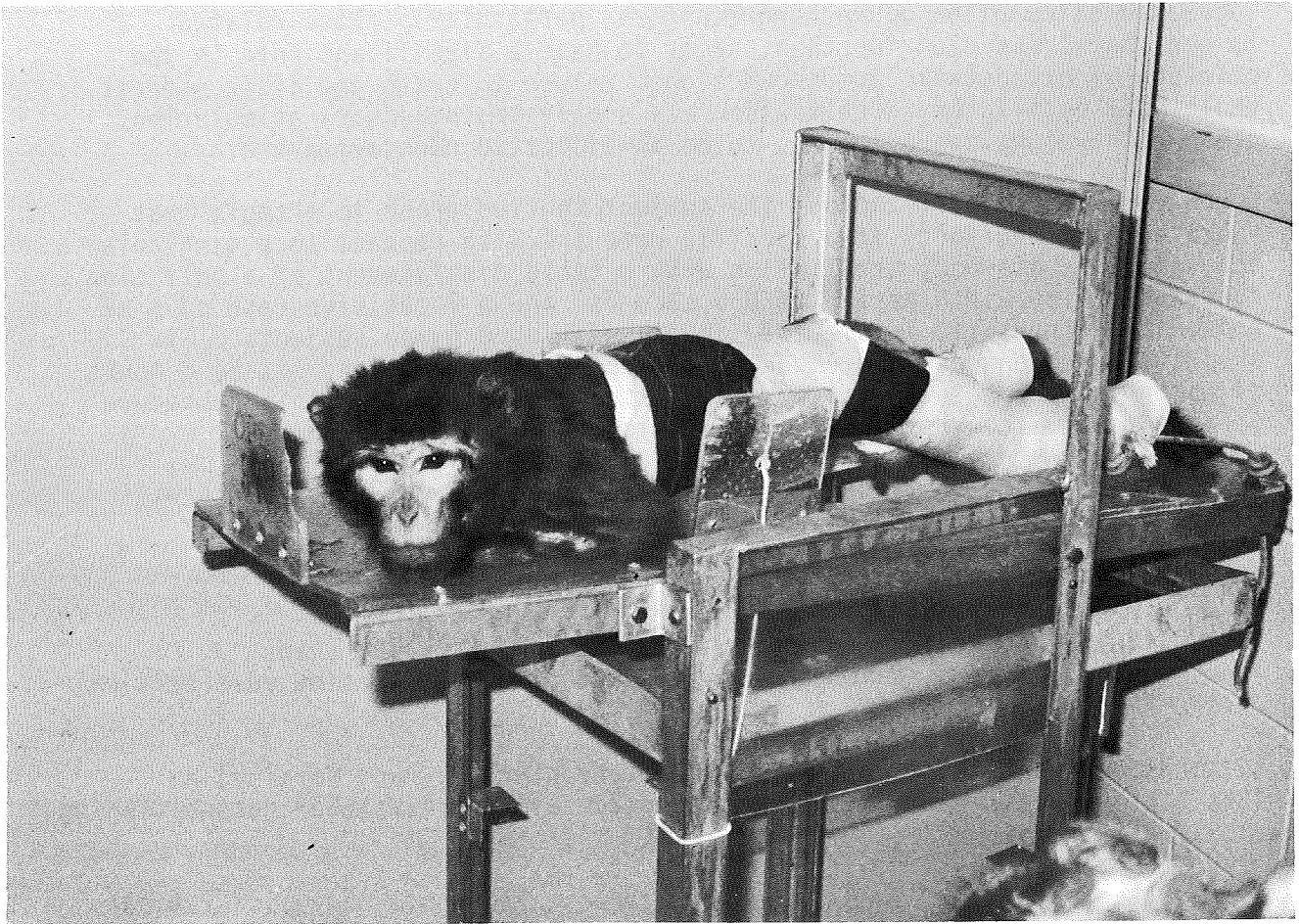
During whole-body oscillation, the subject is tied prone to a table that vibrates back and forth at a specific rate and with respect to a particular body axis. Whole-body oscillation with a table displacement of a half sine function (pulse width period of 0.5 seconds) and a repetitive rate of 1 HZ prevented orthostatic intolerance in deconditioned human subjects. Six subjects had been deconditioned by -5° head-down bedrest and six by 6 hours of water immersion to the neck. These studies suggest that this procedure is an effective countermeasure for cardiovascular deconditioning.

These studies will continue along similar lines. Animal experiments will determine the mechanisms responsible for the observed changes.

PUBLICATIONS

1. Bhattacharya, A., Knapp, C. F., McCutcheon, E. P., and Evans, J. M. "Modification of cardiac function by synchronized vasculating acceleration." J APPL PHYSIOL 46:549, 1979.
2. Bhattacharya, A., Knapp, D. V., McCutcheon, E. P., and Cornish, A. "Oscillating acceleration for the prevention of cardiovascular deconditioning." PHYSIOLOGIST 22:4, 1979.
3. Bhattacharya, A. "Cardiovascular responses to whole body oscillation and its therapeutic applications." Biomechanics of Physiological Mechanisms and Injuries, D. M. Ghista, Ed., Oxford, 1979.

Stone
12-11



Rhesus monkey in a horizontal body cast.

199-20-12-11

AUG 1980

MECHANISM OF CARDIOVASCULAR DECONDITIONING IN THE UNANESTHETIZED PRIMATE

H. L. Stone (University of Oklahoma College of Medicine)

An animal model has been developed which mimics in part the events that have been shown to occur with bedrest in human subjects, namely a reduction in blood volume and a loss of orthostatic tolerance.

Data gathered to date indicate that prolonged weightlessness may cause a loss of muscle cells in the heart and alter the reflex adjustments of the circulation to a changing environment such as the return to Earth from space.

The adult rhesus monkey (*Macaca mulatta*) will be used to define the cardiovascular changes that occur during 14 to 30 days of horizontal casting. The carotid sinus and aortic arch will be denervated to examine their roles in the control of circulation in the deconditioned state.

Fluid replacement will also be used in an effort to study the renal and reflex adjustments to volume expansion.

PUBLICATIONS

1. Dickey, D. T., Teoh, K. K., Sandler, H., and Stone, H. L. "Changes in blood volume and response to vasoactive drugs in horizontally casted primates." *PHYSIOLOGIST*, SUPPLE 22:S-27, 1979.

Greenleaf
12-12



Test subject prepared for acceleration in the cab of the centrifuge.

EFFECTS OF FLUID AND ELECTROLYTE SHIFTS ON METABOLISM AND +G_z ACCELERATION TOLERANCE

J. E. Greenleaf (NASA-ARC)

It appears that endurance-trained athletes exhibit significantly reduced orthostatic tolerance when compared to untrained men. Their tolerance to head-to-foot (+G_z) acceleration, however, seems unimpaired. In an effort to understand the physiological mechanism involved in the body's adaptation to weightlessness, this project investigates the effect of dynamic (isotonic) exercise training on responses to +G_z acceleration and tilt-table stresses in normal men and women.

Both bedrest and water immersion reduce tolerance to +G_z acceleration and to tilt-table. Because both models result in a total body dehydration, this study emphasizes fluid-electrolyte shifts and their relationships to tolerance. Oral rehydration after bedrest significantly attenuates the large decrease in tolerance to acceleration post-bedrest. Preliminary findings from subjects exposed to short-term training periods in hot and normal temperatures show that exercise did not make a difference in tolerance to +G_z acceleration.

Future studies will measure orthostatic, acceleration, and exercise tolerance in endurance-trained athletes and in normal untrained subjects before and after water-immersion.

PUBLICATIONS

1. Brock, P. J., Sciaraffa, D., and Greenleaf, J. E. "Effect of physical training in cool and hot environments on +G_z acceleration tolerance in women." *PHYSIOLOGIST* 22:S41-S42, 1979.
2. Convertino, V. A., Greenleaf, J. E., and Bernauer, E. M. "Role of thermal and exercise factors in the mechanism of hypervolemia." *J APPL PHYSIO RES ENVIRON EXERCISE PHYSIOL* 48:657-664, 1980.
3. Greenleaf, J. E., Van Beaumont, W., Brock, P. J., Montgomery, L. D., Morse, J. T., Shvartz, E., and Kravik, S. "Fluid-electrolyte shifts and thermoregulation: Rest and work in heat with head cooling." *AVIAT SPACE ENVIRON MED* 51:747-753, 1980.

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199-20-12-15

SEP 1980

EFFECTS OF CORONARY ARTERIAL DISEASE ON RESPONSES TO SIMULATED SPACEFLIGHT

D. C. Harrison (Stanford University Hospital)

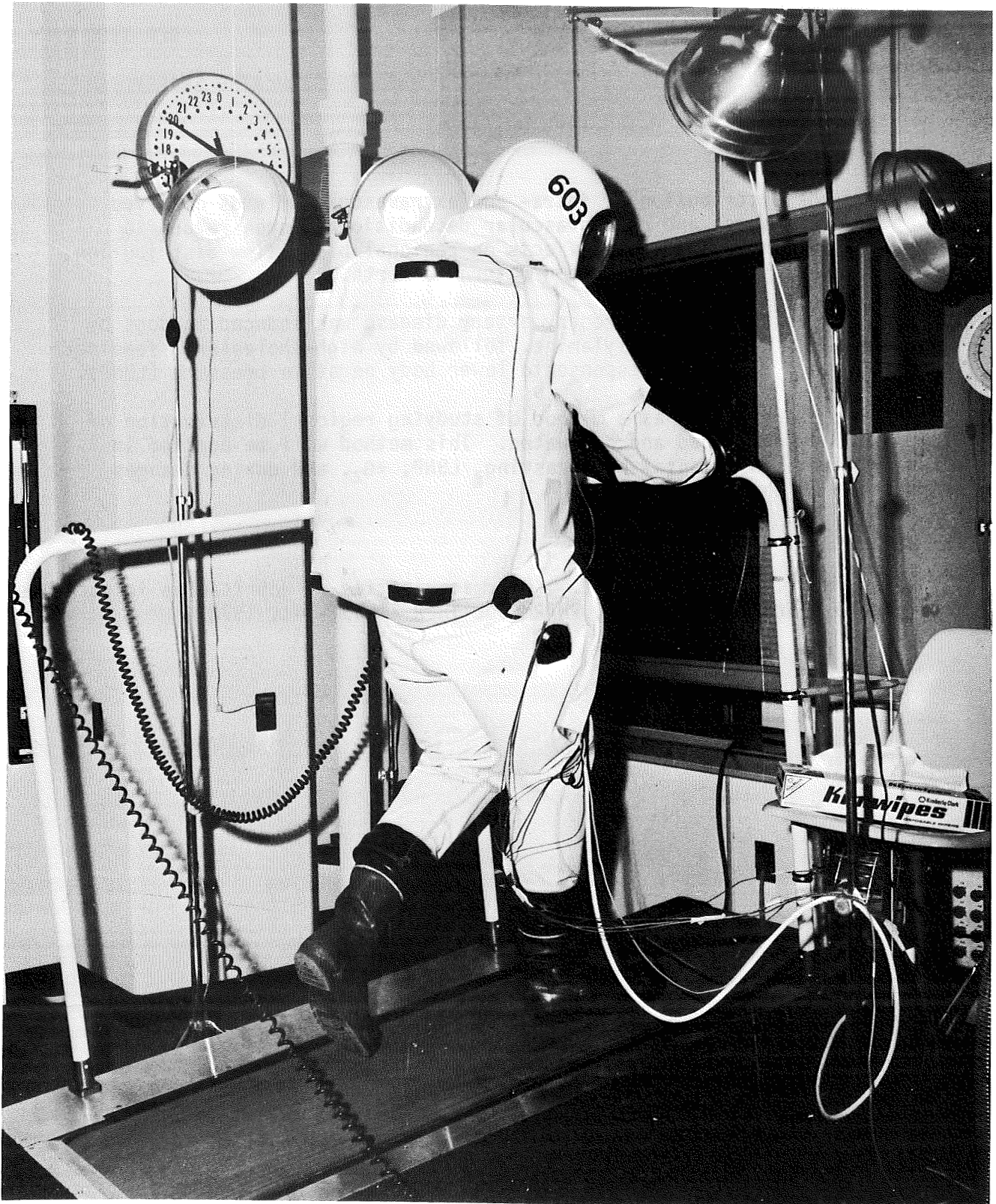
Changes in the distribution of intra- and extravascular fluids observed during weightlessness and cardiovascular deconditioning upon return to Earth appear to have important effects on regional blood flow distribution, both during weightlessness and upon return to Earth.

For this new task, diffuse coronary artery disease was induced in dogs by injection of an irritant, allylamine, followed by high-cholesterol feeding. These dogs have a reduced response to lower body negative pressure (LBNP).

Radioactive microspheres as a method of studying regional distribution of flow have been developed and evaluated. This method will be applied in the heart during horizontal body casting, LBNP, +G_z, and during changes of position of the body.

PUBLICATIONS

1. Kates, R. E. and Leier, C. V. "Pharmacokinetics of dobritamine in patients with severe heart failure." CL PHARMACOL THER 24:537-541, 1978.



Human performance testing: Space suit test -- walking on treadmill.

PHYSIOLOGICAL COSTS FOR ACHIEVING AND MAINTAINING WORK FITNESS

W. C. Alexander (NASA-KSC)

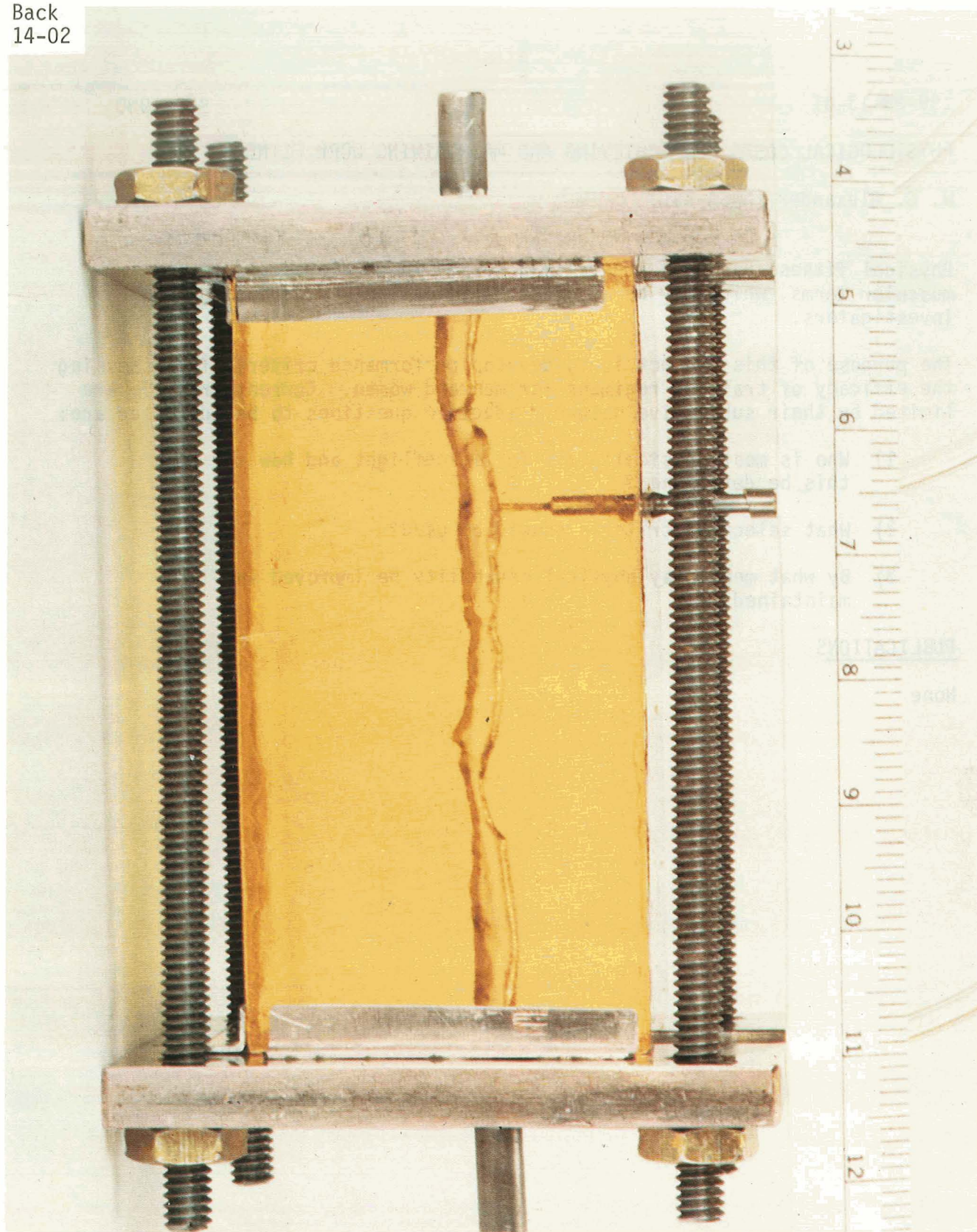
Physical fitness has been generally assessed in cardiovascular-pulmonary-muscular terms, which may be an oversimplification, according to the investigators.

The purpose of this project is to develop performance criteria for assessing the efficacy of training regimens for men and women. Current criteria are limited by their subjective nature. Specific questions to be addressed are:

- 1) Who is most physically fit for spaceflight and how may this be determined?
- 2) What selection criteria should be used?
- 3) By what means may physical capability be improved and maintained?

PUBLICATIONS

None



Polyurethane casting of an atherosclerotic main coronary vessel from a human cadaver study. The length of the relatively short vessel section between the pressure tap shown and the pressure tap in the metal plate on the right side was 46 mm; the upstream diameter was 3.2 mm; and the smallest diameter was about one-half the upstream diameter, an amount of constriction that usually would not be considered clinically significant.

199-20-14-02

NOV 1980

THEORETICAL AND EXPERIMENTAL STUDY OF DISEASED CORONARY ARTERIES UNDER STRESS

L. H. Back (JPL-CIT)

Theoretical and experimental models are developed to explore the hydrodynamics of blood flow in individuals with diseased coronary arteries when subjected to various types of stress such as abnormal accelerations, redistribution of blood volume, and re-entry from space.

A computer model for blood flow through diseased arteries and an experimental apparatus to bench test the flow through negative replicates of vessel casts have been developed. These two techniques are applied to study flow data from animals with induced arterial disease.

Techniques have been developed to determine the in vivo relationship of pressure-drop to flow-rate in animals.

PUBLICATIONS

None

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2. SPACE MOTION SICKNESS

UPN	PI	SHORT TITLE
199-20-21-02	Homick	Mechanisms Underlying Motion Sickness
199-20-21-03	Parker	Intralabyrinthine Fluid Pressure Dynamics
199-20-21-04	Igarashi	Semicircular Canal and Otolith Interaction
199-20-21-05	Correia	Vestibular Primary Afferents
199-20-21-06	Anderson	Posture Control Mechanism
199-20-21-09	Lackner	Development of Predictive Indices
199-20-22-03	Mehler	Vestibular Anatomy and Physiology
199-20-22-04	Goldberg	Vestibular Physiology of Squirrel Monkeys
199-20-22-05	Daunton	Sensory Interactions of Efferent Influence
199-20-22-06	Bizzi	Cortical Cerebellar Eye-Head Coordination
199-20-22-07	Hein	Neural Pathways of Orientation
199-20-22-08	Markham	Otolith-Visual Center Connections
199-20-22-09	Young	Etiology and Prevention Space Motion Sickness
199-20-22-10	Cowings	Biofeedback
199-20-22-11	Brizzee	Histochemistry CNS Emetic Apparatus
199-20-22-12	Lim	Gravity Receptors Environmental and Genetic Effects
199-20-22-13	Jex	Vestibular System Math Model
199-20-22-14	Wilson	Vestibulocollic-Otolith Reflexes

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INTRODUCTION

Symptoms of vertigo, nausea, and disorientation usually appear shortly after the initiation of active movements in weightlessness and last for three to seven days. At present, the most generally accepted theory underlying this motion sickness is the "sensory conflict hypothesis." According to this theory, symptoms result from sending unfamiliar or unexpected combinations of sensory signals in the central nervous system.

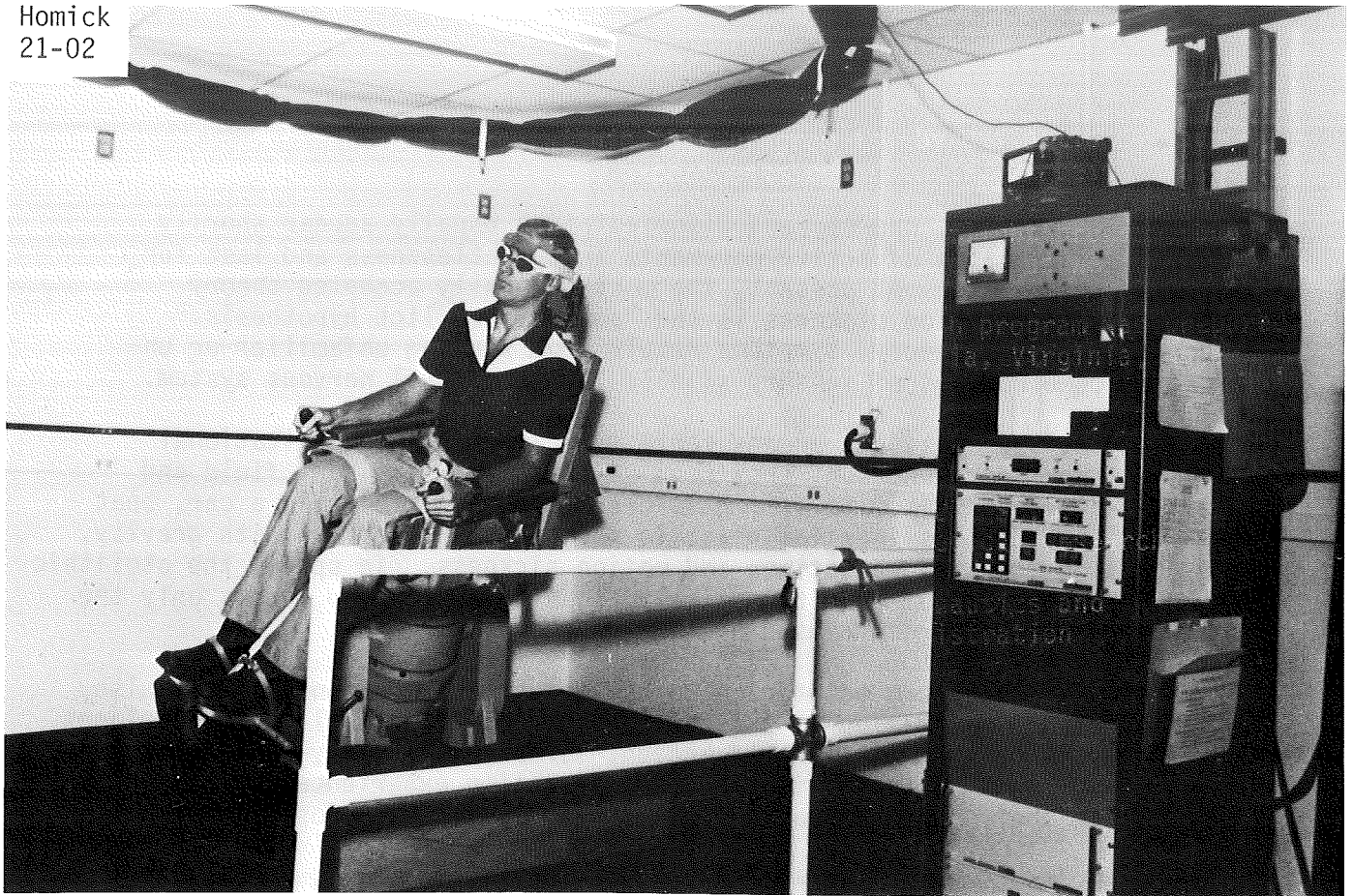
For example, the otolithic organs sense the direction of gravitational force. For proper function, they require (1) a gravitational field and (2) the absence of any interfering forces. A person riding in a car, boat or airplane undergoes inertial reactive forces that interfere with gravity, thus causing illusory sensations and motion sickness. In space, the otolithic organs are deprived of gravity entirely, leaving as sensory inputs only the inertial relative forces caused by head and body movements.

Mechanisms of long-term adaptation to the weightless environment must also be elucidated. Adaptation is thought to occur as the visual system replaces vestibular functions. This would account for observed carry-over adaptation during postflight tests and for the disorientation experienced by astronauts upon moving their heads or walking with their eyes closed postflight.

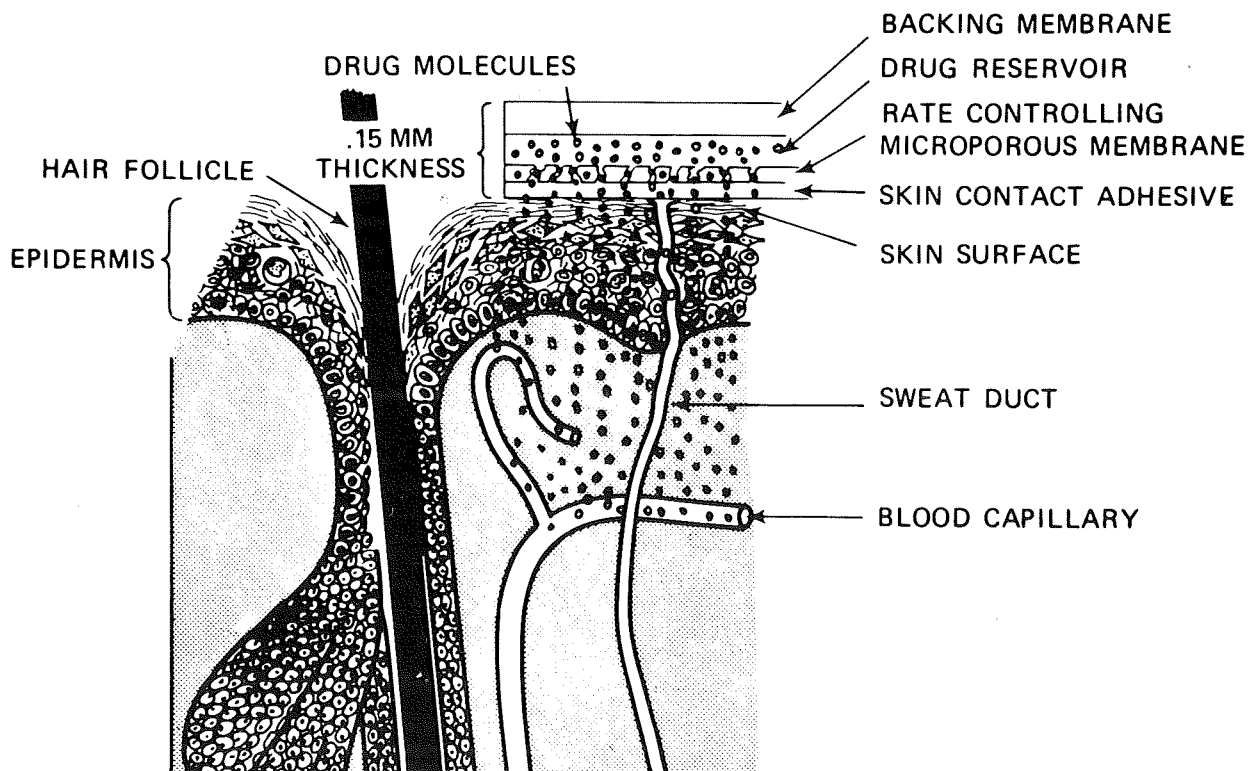
Because motion sickness undermines maximum work performance, particularly in short-duration flights, it will be very important to develop techniques and criteria for selecting crew members for future flights. It is interesting, though disheartening, that none of the preflight test data on the Skylab astronauts correlated with the actual occurrence of SMS symptoms in flight.

Attempts to pre-adapt the Skylab crewmen by rotating chair and/or exposures to parabolic flight have not been visibly useful. The use of anti-motion sickness drugs to prevent and treat symptoms as they occurred has yielded extremely limited and variable success.

The overall objective of this research program is to develop criteria for crew selection, techniques for preventing symptoms, and methods for effective treatment of symptoms once they occur. Emerging flight experiments will contribute to the validation of the ground-based studies and will attempt to elucidate adaptive mechanisms.



Above: Subject in rotating chair used in vestibular function research.
Below: Diagram of anti-motion sickness drug action.



199-20-21-02

OCT 1980

MECHANISMS UNDERLYING MOTION SICKNESS IN MAN

J. L. Homick and M. F. Reschke (NASA-JSC)

Two major research activities are under way. The first is to identify drugs which provide maximum protection against space motion sickness with minimum side effects. Six drugs have been extensively evaluated, including dermally administered scopolamine. The effectiveness of oral medications is also being tested in susceptible subjects on a zero-gravity plane and in ground-based motion devices.

Secondly, neural mechanisms in man which respond to linear acceleration and which control the major anti-gravity muscles are being investigated, as is vestibular function at the cellular level in small animals.

PUBLICATIONS

None

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INTRALABYRINTHINE FLUID PRESSURE DYNAMICS

D. E. Parker (Miami University)

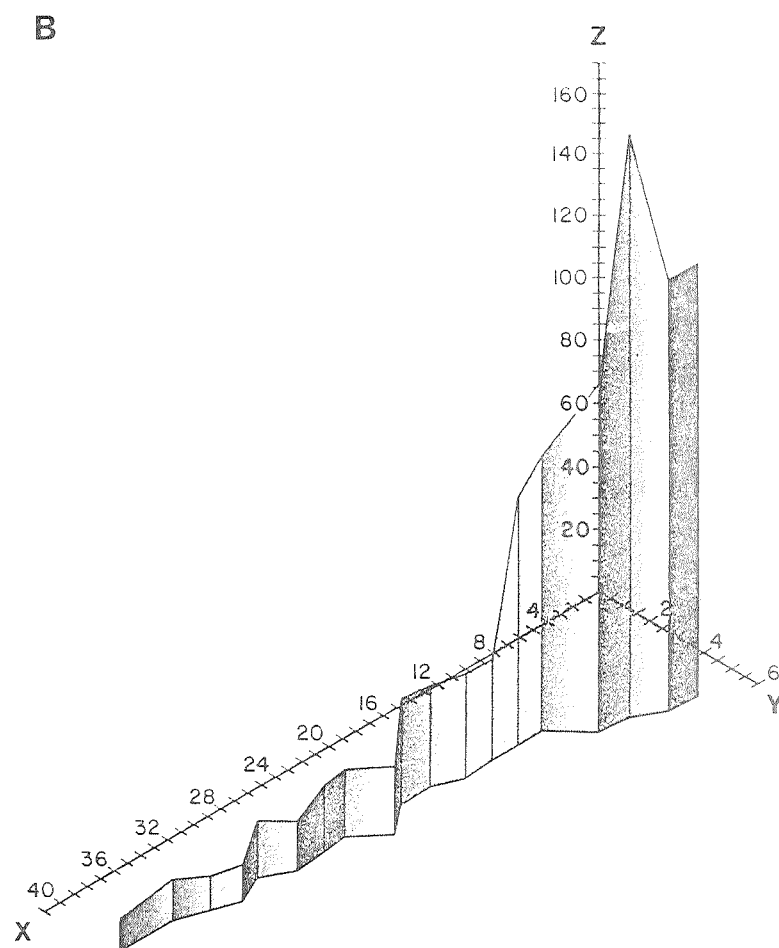
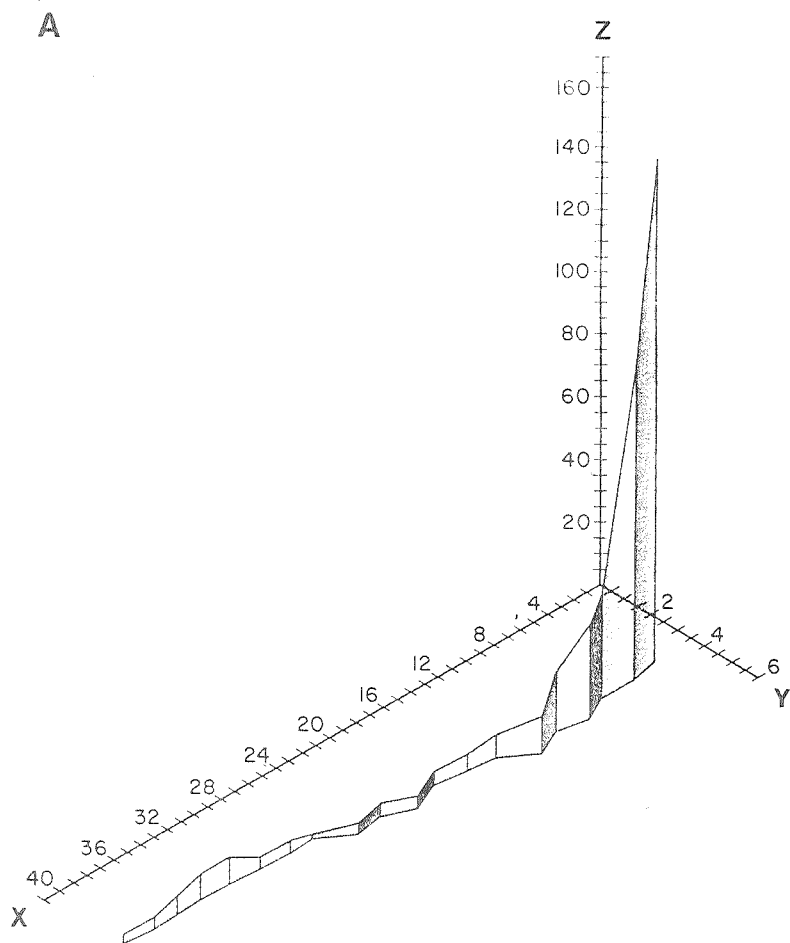
It has been proposed that space motion sickness (SMS) might be associated with a change in vestibular input caused by the large shifts of body fluids that occur when an astronaut enters the weightless environment. The present task investigates whether body fluid shifts contribute to SMS. Changes in motion perception and biochemical properties of the inner ear are examined following body fluid shifts produced by head-down tilt.

Both middle ear impedance and auditory tone detection thresholds change with fluid shifts. However, motion perception appears unaltered. Also investigated are ways in which different individuals respond to different inputs (vestibular, visual, and neck receptor) when they report their orientation in space.

Future studies will examine how easily different people shift their dependence from one type of input to another (e.g., visual to vestibular). Results from these investigations should help develop tests that predict susceptibility to SMS and training procedures that ameliorate the problem.

PUBLICATIONS

1. Parker, D. E., Gullledge, W. L., Tubbs, R. L., and Littlefield, V. M. "A temporary threshold shift for self-motion detection following sustained oscillating linear acceleration." PERCEPT PSYCHOPHYS 23:461-467, 1978.
2. Parker, D. E., Wood, D. L., and Gullledge, W. L. "Self-motion magnitude estimation during linear oscillation: Changes with head orientation and following fatigue." AVIAT SPACE ENVIRON MED 50(1):111-121, 1979.
3. Parker, D. E. "The vestibular apparatus." SCI AM 243(5):118-135, 1980.



Reductions in over-ground gait deviation. Labyrinthectomized squirrel monkeys were exposed to tread-mill run exercise. The exercise group (A) recovered functionally much faster than the non-exercise, control group (B). There was no difference in running time. (X axis, calendar days after surgery; Y axis, running time in seconds; Z axis, severity of ataxia due to surgery.)

ETIOLOGY AND COUNTERMEASURES OF SPACE MOTION SICKNESS

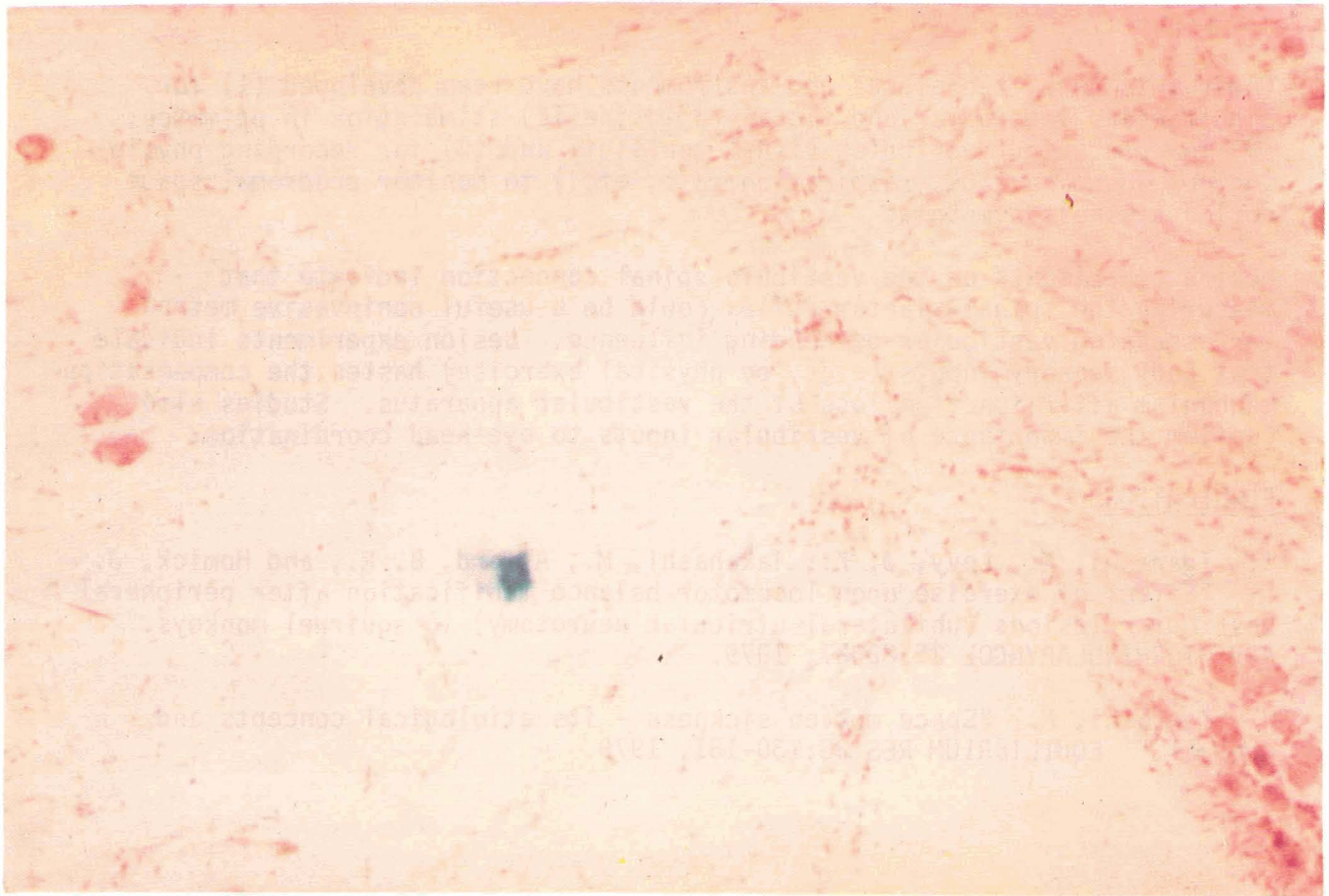
M. Igarashi (Baylor College of Medicine)

Under this task, techniques and instruments have been developed (1) for simultaneous vestibular and visual (optokinetic) stimulation in primates; (2) for producing vestibular-visual conflict; and (3) for recording physiological function (ECG, respiration rate, etc.) to monitor prodromal space motion sickness symptoms.

Lesion experiments on the vestibulo-spinal connection indicate that measuring the spinal-plantar reflex could be a useful noninvasive method for assessing vestibular descending influence. Lesion experiments indicate that body sensory inputs (e.g., by physical exercise) hasten the compensation mechanism after function loss of the vestibular apparatus. Studies also confirm the importance of vestibular inputs to eye-head coordination.

PUBLICATIONS

1. Igarashi, M., Levy, J. K., Takahashi, M., Alford, B. R., and Homick, J. L. "Effect of exercise upon locomotor balance modification after peripheral vestibular lesions (unilateral utricular neurotomy) in squirrel monkeys." ADV OTORHINOLARYNGOL 25:82087, 1979.
2. Igarashi, M. "Space motion sickness - its etiological concepts and control." EQUILIBRIUM RES 38:130-131, 1979.



A photomicrograph of a transverse section through the brainstem and Scarpa's ganglion of a pigeon in which an alcian blue dye spot was electrophoretically deposited. The spot confirms the location from which action potentials are recorded in a non-barbiturate anesthetized whole-brain pigeon preparation.

ELECTROPHYSIOLOGICAL AND MORPHOLOGICAL STUDIES OF THE VESTIBULAR
AFFERENT AND EFFERENT SYSTEM

M. J. Correia (University of Texas Medical Branch)

Electrophysiological and anatomical studies are being conducted on the vestibular afferent/efferent system of birds and small mammals. These animals have inner ears which are easily accessible for experimental manipulation and produce responses similar to those produced in non-human primates. The understanding of normal physiological vestibular responses will provide a background for comparison with abnormal vestibular responses which have occurred on past space missions and which probably will occur in the future.

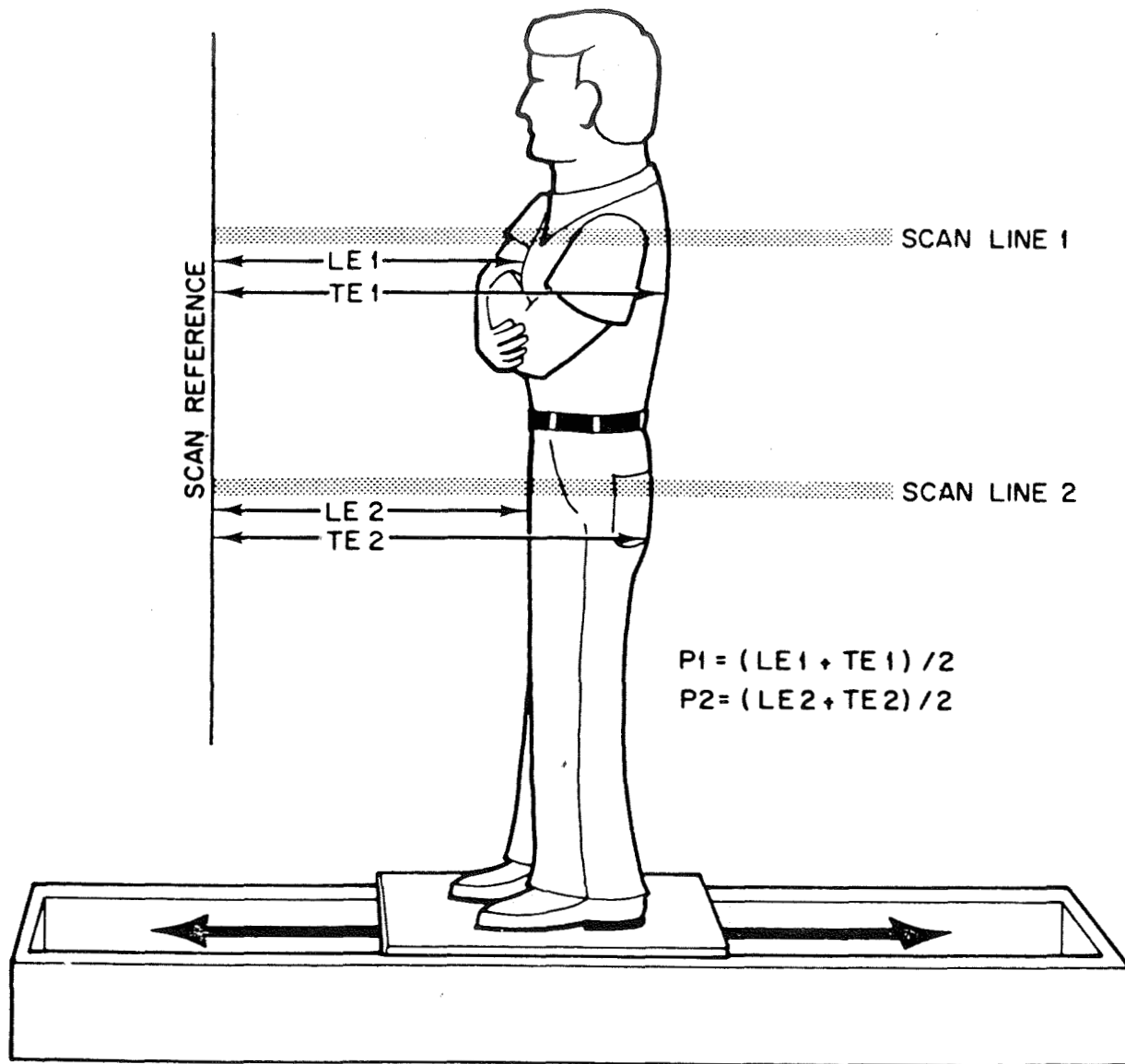
Using histological staining procedures, four discrete clusters of vestibular efferent neurons have been delineated in the pigeon brainstem. Also, auditory and vestibular pathways have been traced using radioactive markers.

A mathematical model explaining the origin of impulses on the vestibular nerve has been developed. Moreover, the way in which sensory information is transferred on vestibular primary afferents has been characterized.

Future research will include electrophysiological studies on the vestibular efferent system and afferent responses of otolith organs to dynamic linear acceleration.

PUBLICATIONS

1. Eden, A. R. and Correia, M. J. "Horseradish peroxidase identification of four separate groups of vestibular efferent neurons in the adult pigeon." NEUROSCI ABSTS 5:18, 1979.
2. Landolt, J. P. and Correia, M. J. "Neurodynamic response analysis of anterior semicircular canal afferents in the pigeon." J NEUROPHYSIOL 43: 1746-1770, 1980.
3. Black, F. O., Correia, M. J., and Stucker, F. J. "Easing proneness to motion sickness" (A. S. Brodoff, ed.) PATIENT CARE 14:114-128, 1980.



The Postural Measurement System. Scan lines are positioned at the hips and the shoulders to record anteroposterior sway. Average position is calculated from the locations of the leading edge (LE) and trailing edge (TE). The arrows on the platform indicate the direction in which the subject is moved to test postural sway responses (from R. O. Andres and D. J. Anderson, AM J OTOLARYNG 1(3):202, 1980.)

EVALUATION OF POSTURAL MECHANISMS UNDER DYNAMIC CONDITIONS

D. J. Anderson (University of Michigan Medical School)

Early emphasis of this study was on the design and development of a hardware and software system which could serve as a complete posture-analysis package. The final version of the posture platform induces postural instability and body sway by moving the subject's base of support back and forth.

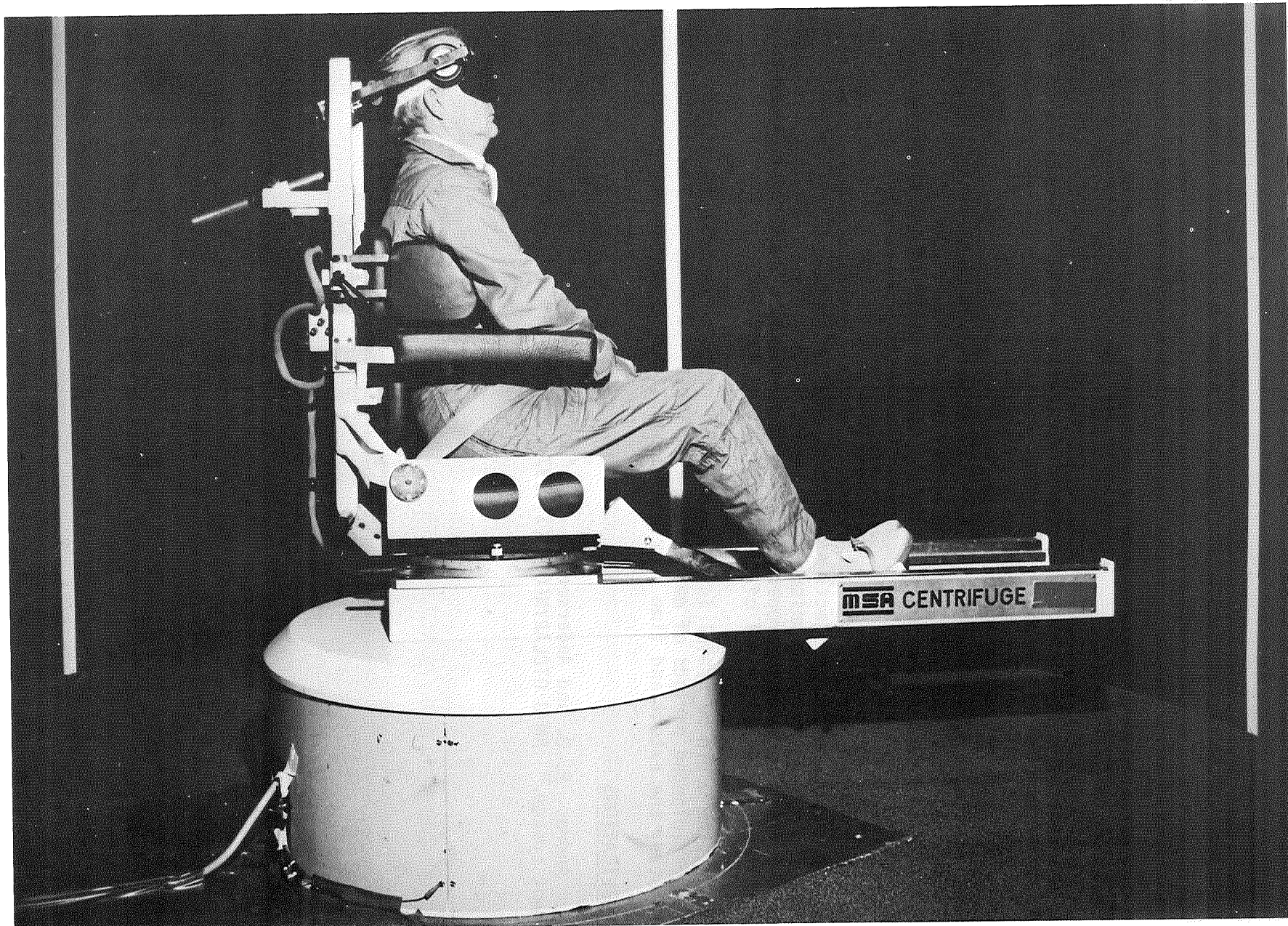
The resultant motions are similar to those encountered in everyday life (e.g., transient steps similar to slipping on ice and pseudorandom motions similar to standing on a moving vehicle). Displacement of the platform and of the subject's hips and shoulders is measured and analyzed.

The most recent emphasis of the project has been the interpretation of data collected from normal subjects and from patients with otological or neurological dysfunction. Techniques from linear systems theory are being employed to describe the dynamic properties of subject response. The result should be a full parameterized model of the human posture system.

The system would be useful in the problem of postural control adaptation after prolonged periods of weightlessness. Spacelab crews will be tested to study the extent and time course of adaptation.

PUBLICATIONS

1. Andres, R. O. and Anderson, D. J. "Designing a better postural measurement system." AM J OTOLARYNGOL 1(3):197-206, 1980.



Sudden-stop vestibulo-visual interaction test.

VESTIBULAR SELECTION CRITERIA DEVELOPMENT

J. R. Lackner (Brandeis University)

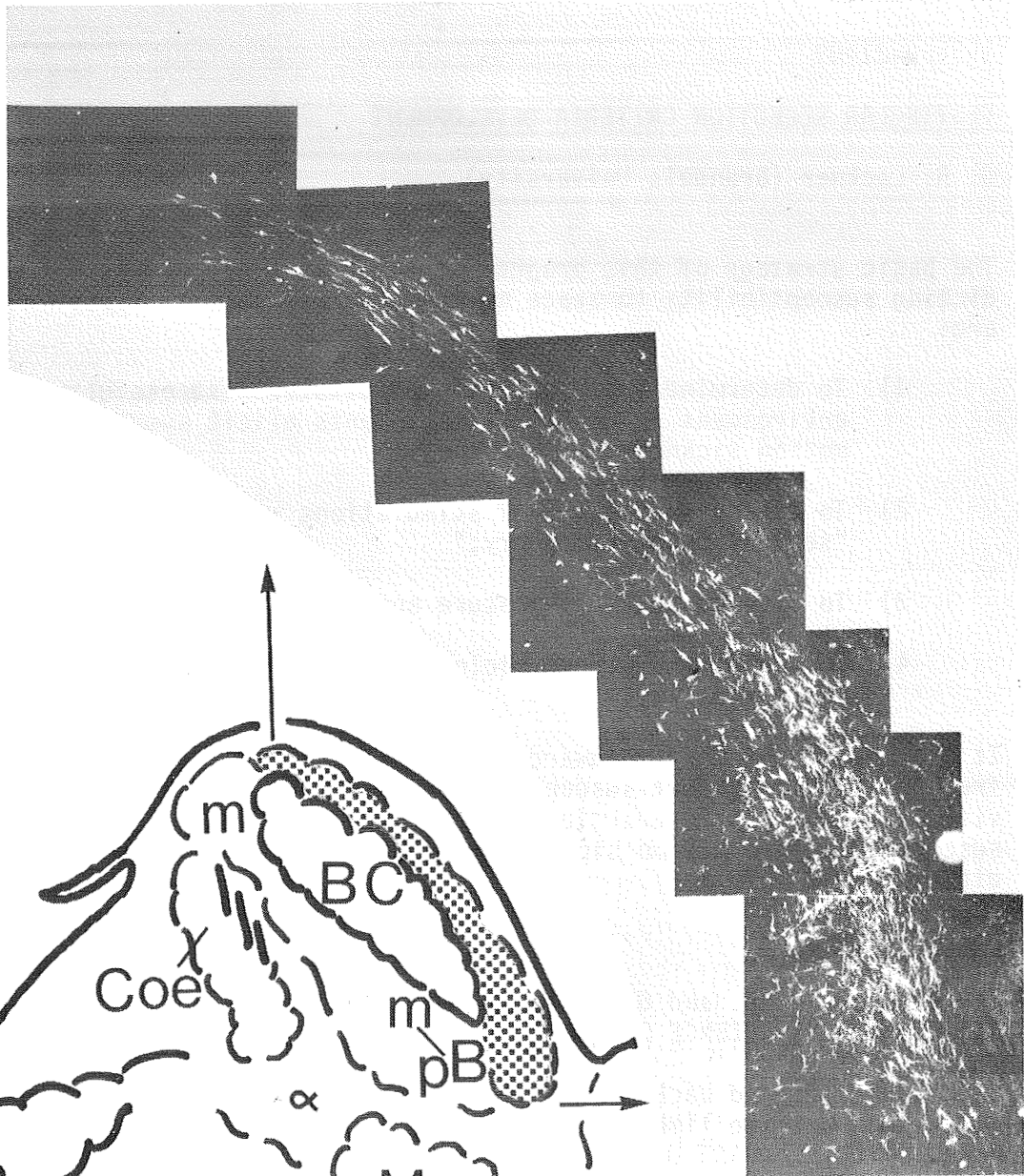
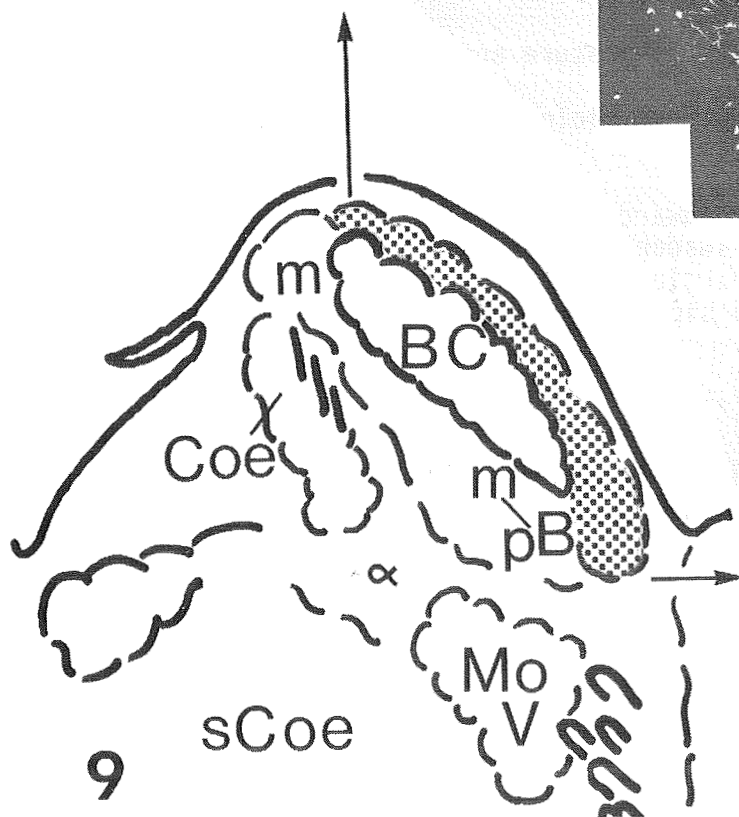
The basic strategy of this project is to develop procedures for predicting susceptibility to space motion sickness (SMS). Specific objectives are:

- 1) To determine why free fall constitutes a stressful motion environment in which head movements elicit symptoms of motion sickness;
- 2) To establish a range of stimulations with which to test the "sensory conflict theory;"
- 3) To develop tests to measure susceptibility to SMS;
- 4) To identify psychophysiological correlates of SMS susceptibility.

It has been found that headward fluid shifts of the magnitude occurring in free fall do not affect susceptibility to motion sickness. A vestibulo-visual sudden-stop interaction test has been developed that measures susceptibility to motion sickness in free fall and under terrestrial conditions.

PUBLICATIONS

1. Lackner, J. R. and Graybiel, A. "Parabolic flight: Loss of sense of orientation." SCIENCE 206:1105-1108, 1979.
2. Mather, J. and Lackner, J. R. "Adaptation to visual displacement with active and passive limb movements: Effect of movement frequency and predictability." QUART J EXP PSYCH 32:317-323, 1980.
3. Graybiel, A. and Lackner, J. R. "A vestibular-visual sudden stop interaction test for rapid assessment of motion sickness manifestations." AVIAT SPACE ENVIRON MED 51:21-23, 1980.



Horseradish peroxidase (HRP)-labeled cells in midbrain. HRP-positive cells outline the nucleus parabrachialis lateralis (dark-field photo montage). Its relationship to other nuclei is shown in the drawing (BC, brachium conjunctivum; pBm, nucleus parabrachialis medialis; Coe α , nucleus coeruleus α ; MoV, nucleus nervi trigemini motorius; sCoe, nucleus subcoeruleus).

NEURAL MICROCIRCUITRY OF THE VOMITING TRIGGER ZONES

W. Mehler (NASA-ARC)

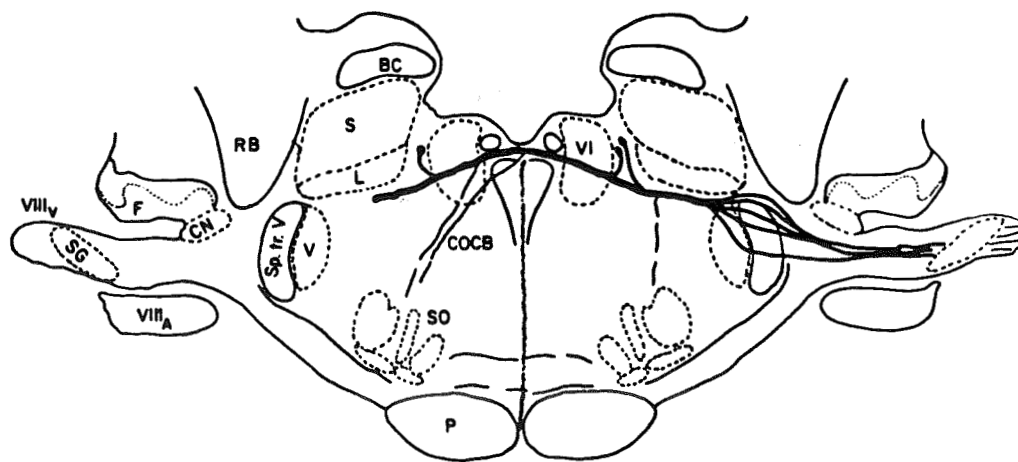
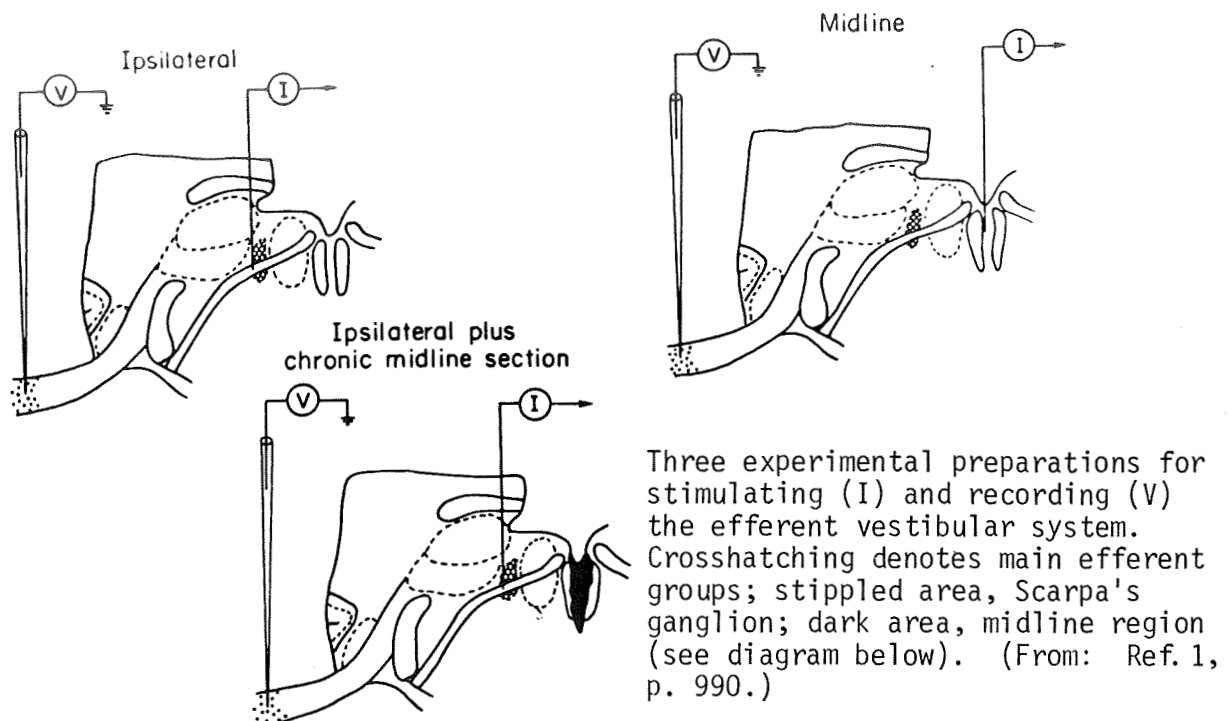
Vomiting, or emesis, is the physiological endpoint to vertigo and malaise in space motion sickness and is chiefly induced by labyrinth impulses transmitted via primary vestibular fibers to the vestibulo-cerebellum. The route between the vestibulo-cerebellum and the vomiting trigger zone (VTZ) in the lower brainstem or the chemoreceptive trigger zone (CTZ) is under investigation.

A possible point of convergence of vestibular and visuo-vestibular impulses, both of which can induce emesis, has been identified as certain parts of the accessory inferior olivary nuclei. The amygdala in the forebrain, which can induce prodromal symptoms of motion sickness as well as emesis when stimulated, has been analyzed neuroanatomically.

Future studies will continue along these lines of investigation. Micro-injection studies of the local neural circuitry of structures in the VTZ and CTZ will be expanded. The possibility of a link between the amygdala and brainstem VTZ and/or CTZ will be studied.

PUBLICATIONS

1. Mehler, W. R., Mantyh, P., and Phelan, K. D. "Afferent connections of the amygdala in the cat." SOC NEUROSCI ABSTR 5:279, 1979.
2. Phelan, K. D. and Mehler, W. R. "Vestibulo-cerebellar afferents from the inferior olive and the vestibular nuclear complex." SOC NEUROSA ABSTR 5:106, 1979.
3. Mehler, W. R. "Subcortical afferent connections of the amygdala in the monkey." J COMP NEUROL 190:733-762, 1980.



Vestibular and auditory efferent pathways. (BC, brachium conjunctivum; CN, cochlear nuclei; COCB, crossed olivocochlear bundle; F, flocculus; L, lateral vestibular nucleus; P, medullary pyramid; RB, restiform body; S, superior vestibular nucleus; SG, Scarpa's ganglion; SO, superior olivary complex; Sp. tr. V and V, spinal trigeminal tract and nucleus, respectively; VI, abducens nucleus; VII, facial genu; VIII_A and VIII_V, auditory and vestibular nerves, respectively. From: PUB 1, p 993)

PHYSIOLOGY OF THE VESTIBULAR SYSTEM

J. M. Goldberg (University of Chicago)

The ultimate goal of this project is to determine the functional contributions of peripheral and central vestibular neurons to the overall operation of the vestibular system.

Investigations using the squirrel monkey showed that the two types of primary vestibular neurons exhibited significantly different responses to electrical stimulation, one being ten times more sensitive than the other.

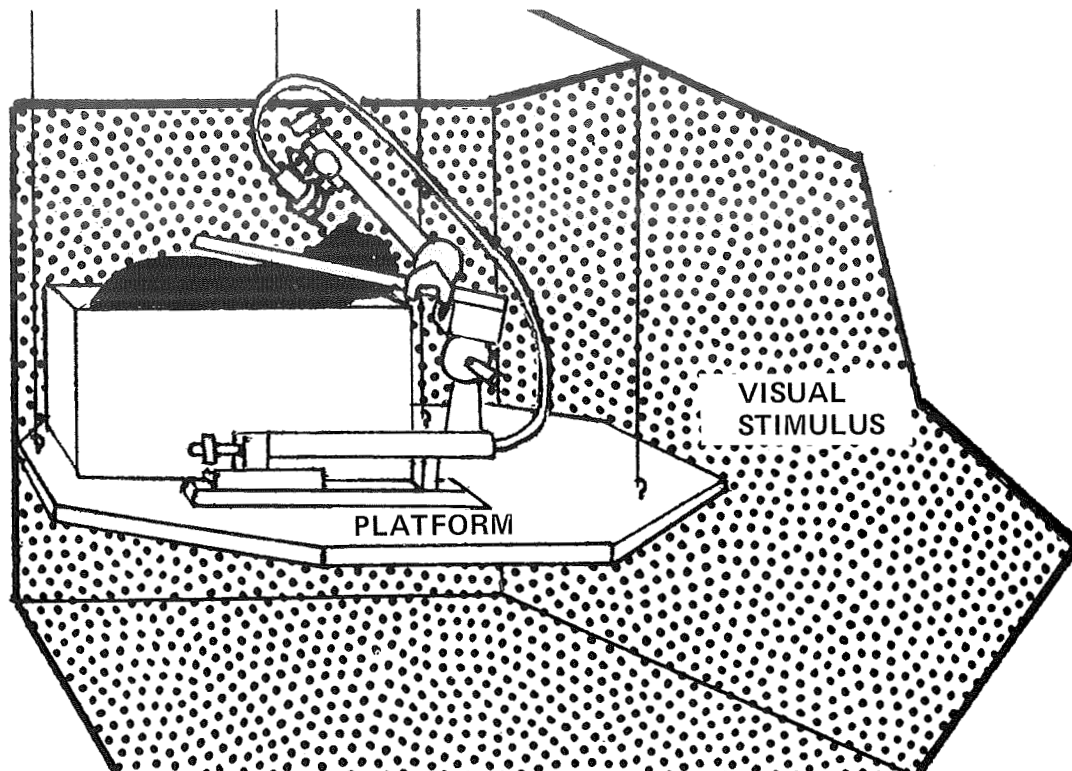
There is evidence that the vestibulo-ocular reflex (VOR) can be modified by visual stimuli to partially compensate for the loss of input from a single horizontal canal.

Studies of nystagmus in response to earth-horizontal rotation in anesthetized monkeys indicate persistent horizontal and vertical nystagmus (responses to rotation about the horizontal and sagittal planes, respectively) are not functions of semicircular canal stimulation.

Three projects currently being pursued are: (a) intracellular studies of vestibular afferents in the chinchilla; (b) further investigation of thick and thin afferents; and (c) studies of the role of efferent control in vestibular function.

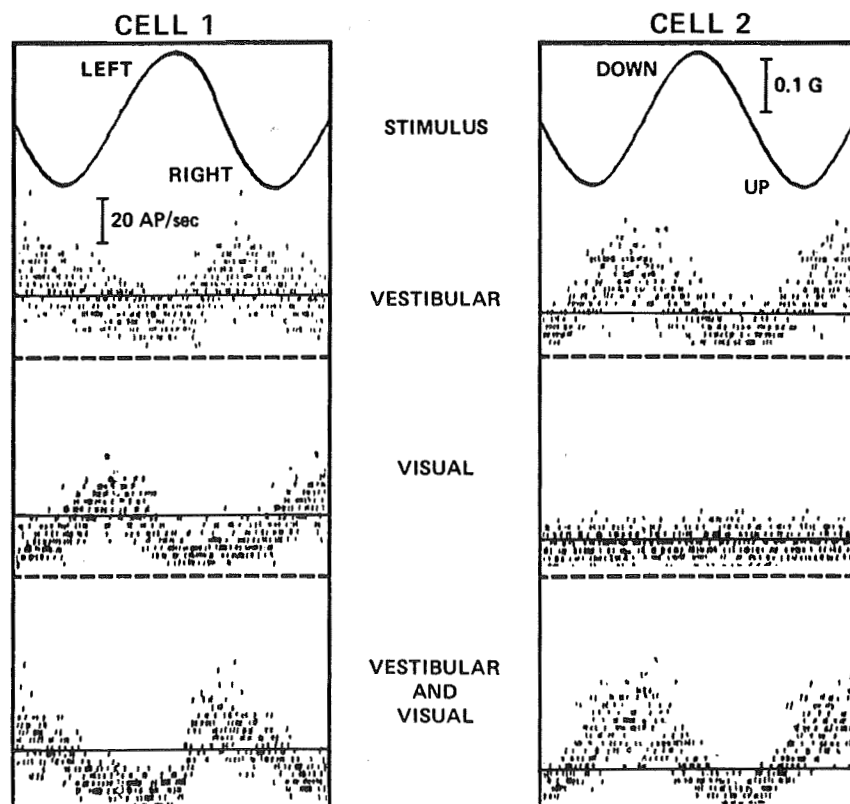
PUBLICATIONS

1. Goldberg, J. M. and Fernandez, C. "Efferent vestibular system in the squirrel monkey: Anatomical location and influence on afferent activity." J NEUROPHYSIOL 43(4):986-1025, 1980.
2. Goldberg, J. M. "Vestibular receptors in mammals: Afferent discharge characteristics and efferent control." PROGR BRAIN RES 50:355-67, 1979.
3. Goldberg, J. M. and Fernandex, C. "Conduction times and background discharge of vestibular afferents." BRAIN RES 122:545-50, 1977.



Above: Cat in visual vestibular studies. The cat is placed on a platform suspended by springs. Accelerometers mounted on the platform record simultaneously the platform's accelerative forces and the cell responses. The visual stimulus (cut away to show cat) surrounds the cat and is also suspended by springs.

Below: Response of two cells to stimuli. Recordings from two different cells in the vestibular nucleus indicate sensitivity of both cells to vestibular stimuli. However, only Cell 1 is also responsive to visual stimuli.



199-20-22-05

OCT 1980

FUNCTIONAL SIGNIFICANCE OF SENSORY INTERACTION AND EFFERENT INFLUENCE
ON THE VESTIBULAR SYSTEM

N. G. Daunton (NASA-ARC)

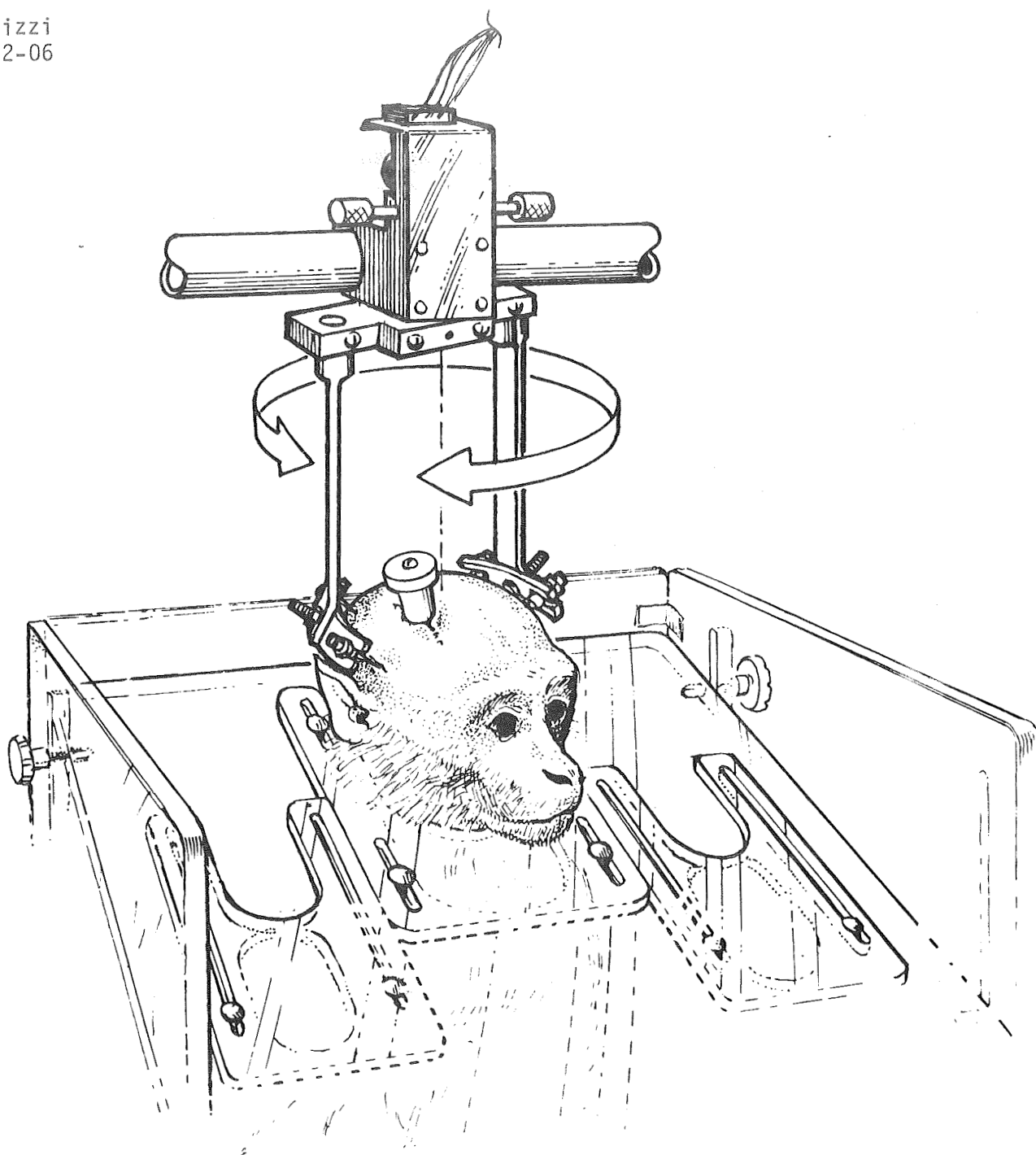
The objective of this research is to understand the neurosensory adaptation to the weightless environment and to develop more effective countermeasures to motion sickness than are currently available.

Single cell recordings in the vestibular nuclei of cats have indicated that their motion perception is similar to man's. Other studies indicate that the cat's hormonal responses are similar to man in motion-sickness-inducing situations. In both species, susceptible individuals show an increase in antidiuretic hormone, while nonsusceptible individuals show little change.

Work on visual-vestibular interaction in vestibular nuclei of the cat will continue. Other related brain areas will also be explored and similar recordings in squirrel monkeys will be initiated.

PUBLICATIONS

1. Daunton, N. G. and Thomsen, D. "Visual modulation of otolith-dependent units in cat vestibular nuclei." EXP BRAIN RES 37:173-176, 1979.
2. Suri, K., Crampton, G. H., and Daunton, N. G. "Motion sickness in cats: A symptom rating scale used in laboratory and flight tests." AVIAT SPACE ENVIR MED 50:614-618, 1979.



Eye-head coordination studies. When a visual target is suddenly presented, it attracts the monkey's attention and initiates an orderly sequence of eye and head movements. A fast eye movement, called a saccade, turns the eyes so that the target is centered on the fovea, the most sensitive part of the retina. Some 20 - 40 msec later, the monkey's head begins turning in the same direction. During this head movement, the eyes must counter-rotate to keep the target fixated. The amount of head-turning is transmitted to a recorder by the lightweight apparatus clamped to monkey's head. Eye movement is recorded by electro-oculography.

ROLE OF CORTICAL AND CEREBELLAR AREAS IN THE CONTROL OF EYE-HEAD COORDINATION IN MONKEYS

E. Bizzi (Massachusetts Institute of Technology)

Conventional models of sensorimotor coordination are unable to account for the interplay between posture and distance receptors or to deal with the role of the organism's own efferent output. The goal of this investigation is to understand how sensorimotor coordination develops and is maintained under normal and conflicting sensory inputs.

Studies of pre-oculomotor cells show that saccades (or twitching eye movements) are generated without any information on intended head movement. These cells receive information only about actual head movement. Cells that are related to head movement have been identified and localized, but these cells do not receive any information about eye movements or positions.

In future studies, anti-dromic stimulation will be used to identify axons of head-related cells in the spinal cord. Thus, the role of descending commands in the control of head movements will be determined.

Studies of arm trajectories in monkeys will continue the investigation of sensorimotor coordination.

PUBLICATIONS

1. Polit, A. and Bizzi, E. "Characteristics of motor programs underlying arm movements in monkeys." J NEUROPHYSIOL 42:183-194, 1979.
2. Bizzi, E. and Polit, A. "Processes controlling visually evoked movements." NEUROPSYCHOLOGIA 17:203-213, 1979.
3. Bizzi, E. "Strategies of eye-head coordination." In: Reflex Control of Posture and Movement, Granit and Pompeiano, eds. PROGR BRAIN RES 50, 1979.

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GROWTH AND MAINTENANCE OF NEURAL PATHWAYS UNDERLYING ORIENTATION

A. Hein (Massachusetts Institute of Technology)

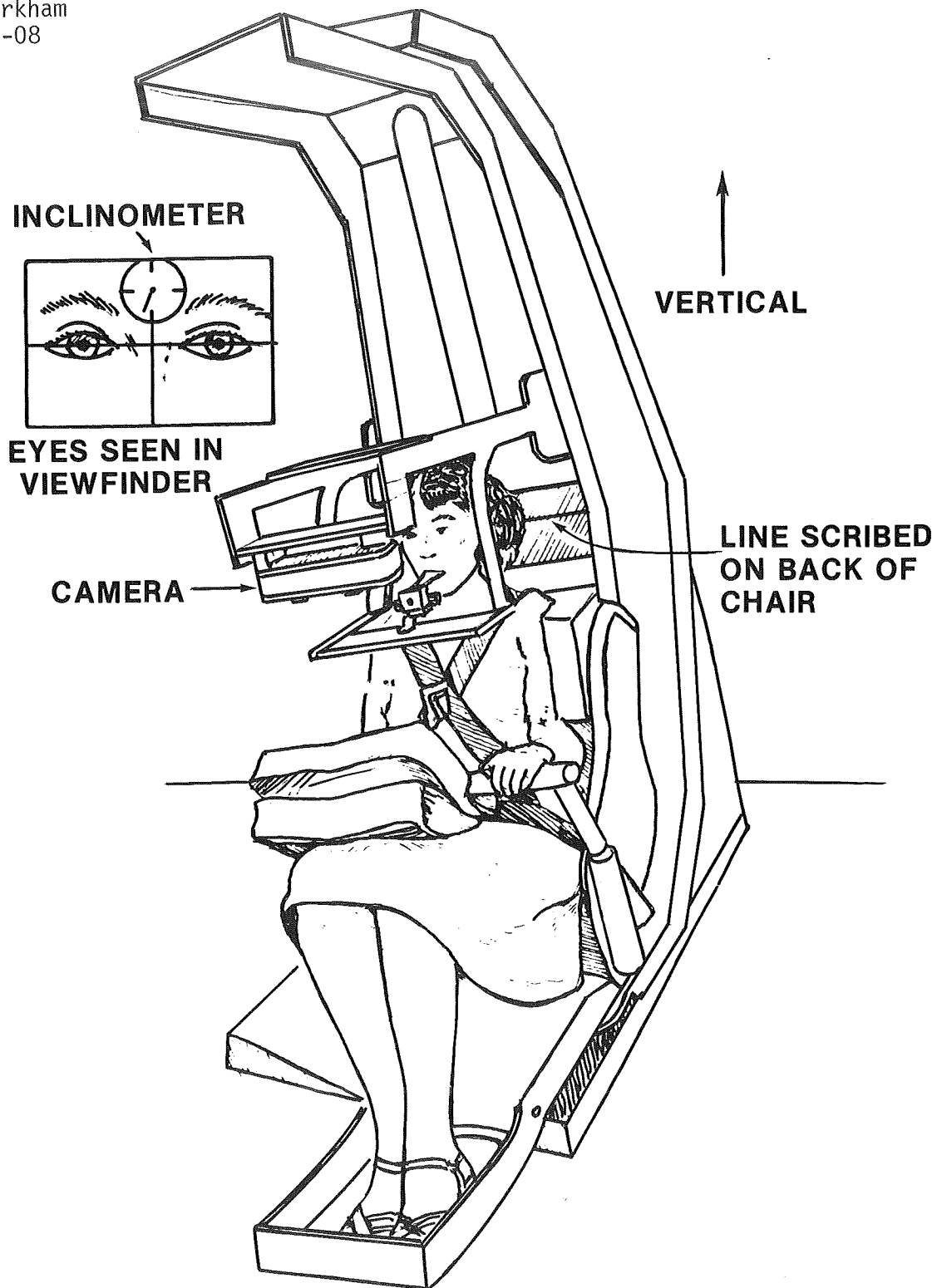
The overloading of an organism's ability to distinguish self-motion sensory inputs from environmental sensory inputs is a major cause of disorientation. The neural substrates involved in this ability are being investigated.

Studies show that eye movements play an essential role in the acquisition of visual-motor skills. Sensory input from extraocular muscles is very important in the initial development of and the ability to localize objects in space.

Studies of these systems will continue in vestibulectomized cats.

PUBLICATIONS

1. Hein, A., Vital-Durand, F., Salinger, W., and Diamond, R. "Eye movements initiate visual-motor development in the cat." SCIENCE 204:1321-1322, 1979.
2. Graybiel, A. M. and Ragsdale, C. W. "Fiber connections of the basal ganglia." PROG IN BRAIN RES 51:239-283, 1979.
3. Hein, A. "Movement in acquiring visual space perception and visually coordinated behavior." In: Visual Coding and Adaptability. C. S. Harris (ed.), Lawrence Erlbaum Associates, Hillsdale, NJ, 1980, pp 51-68.



Rotating chair. Motor-driven chair rotates subject 360° about the naso-occipital axis. Camera is fixed to apparatus and rotates with the subject. Centers of pupils are aligned with horizontal line etched on camera view finder. Position of eyes relative to this line remains constant during rotation. Photographs are taken at each 10°.

(Reprinted with permission from Markham, ACTA OTOLARYNGOL 87:491,1980.)

OTOLITH-VISUAL CENTER CONNECTIONS

C. H. Markham (University of California School of Medicine)

Normally, the utricle in the inner ear reflexly controls torsional eye movements (i.e., when the head tilts to one side, the eyes roll in the opposite direction, helping to maintain a stable image on the retina). This research effort delineates this reflex, called ocular counterrolling (OCR), in normal persons and persons with labyrinths surgically destroyed during tumor removal. Thus, possible problems related to OCR under space-flight conditions may be anticipated.

Studies of OCR during dynamic rotation have led to criteria which differentiate normal persons from those with unilateral vestibular nerve sections. These criteria are applied to OCR profiles, which are obtained from subjects rotated to 90° to each side while having both eyes photographed at each 10°. Distinctly abnormal OCR profiles of subjects who are declared normal by conventional vestibular tests are confirmed abnormal by clinical tests.

During static tilt, however, OCR is not stable, varying about 3°. Under these conditions, the OCR of normal persons and patients with vestibular nerve sections does not differ.

Studies of dynamic OCR will be continued, with emphasis on detection of labyrinthine, vestibular nerve, brain stem, and cerebellar abnormalities. Procedures are being developed to process the data with computerized imaging techniques. Quantification of the criteria of abnormality are also under way.

PUBLICATIONS

1. Diamond, S. G. and Markham, C. H. "Ocular counterrolling during constant velocity roll in normal humans and in patients with unilateral VIII nerve lesions." NEUROSCI ABST 5:706, 1979.
2. Diamond, S. G., Markham, C. H., Simpson, N., and Curthoys, I. S. "Binocular counterrolling in humans during dynamic rotation." ACTA OTOLARYNGOL 87:490-98, 1979.
3. Diamond, S. G. and Markham, C. H. "Binocular counterrolling in humans during sustained body tilt." NEUROSCI ABSTR 6, 1980.



Subject wearing left-right vision reversing goggles.

ETIOLOGY AND PREVENTION OF MOTION SICKNESS IN SPACE

L. R. Young and C. M. Oman (Massachusetts Institute of Technology)

This work concentrates on neurophysiological and psychophysical mechanisms of motion sickness, as well as its time course and symptomatology. The results of these studies are integrated into a model for the etiology of motion sickness.

Recent significant findings include the discovery of reversed circularvection after adaptation to seeing through prism goggles. Circularvection is a phenomenon arising from the association between normal head rotation and relative scene motion. Thus, a pattern of stripes rotating around a stationary observer soon elicits a compelling sensation of self-rotation in the opposite direction.

Visual as well as vestibular cues influence muscle reflexes during free fall. Habituation to a 90° rotation of the visual field (cross-axis habituation) was absent in monkeys who were passively habituated.

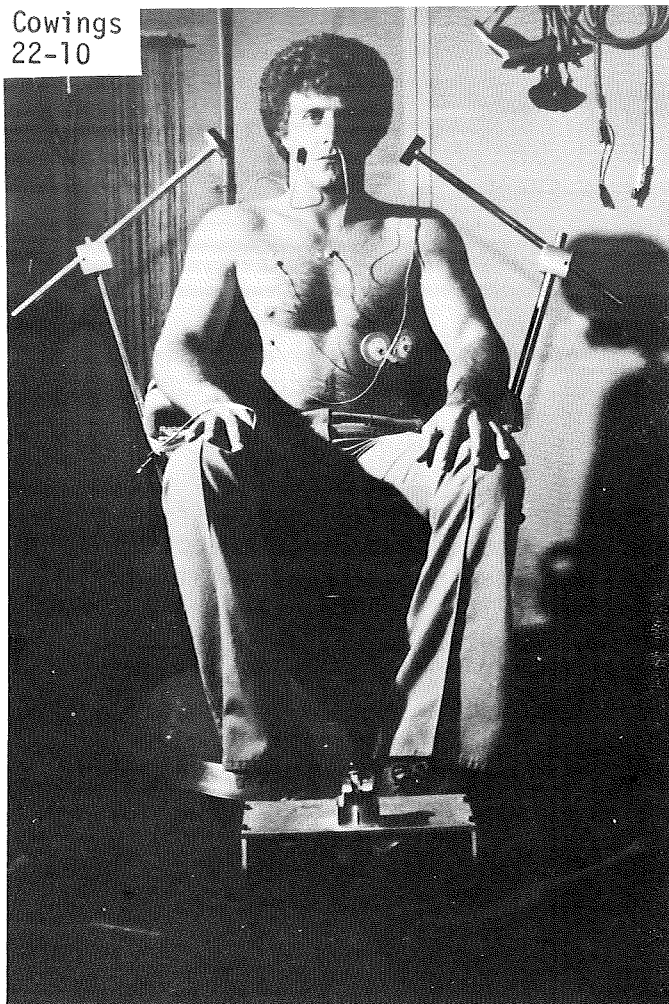
Left-right reversing prisms are used to study both motion sickness and adaptation. Two time constraints are associated with motion sickness: a short time constant (minutes) which causes a rapid increase in symptoms in association with extreme stimuli and a long time constant (hours) which is associated with an accumulation of discomfort over successive stimuli.

Work is also being done on the measurement of ocular counterrolling (a measure of otolith function, especially useful in assessing changes taking place in zero gravity).

PUBLICATIONS

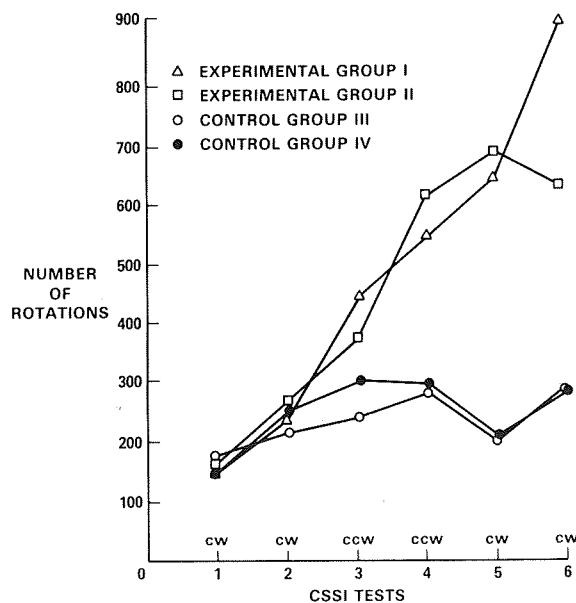
1. Green, L. A. and Young, L. R. "Absence of cross-axis plasticity in the vestibulo-ocular reflex." NEUROSCI ABSTR 5:371, 1979.
2. Oman, C. M., Bock, O. L., and Huang, J. K. "Visually induced self-motion sensation adapts rapidly to left-right visual reversal." SCIENCE 209(4457):706-8, 1980.

Cowings
22-10



Subject seated in rotating chair.
Transducer configuration is displayed.

Number of rotations achieved during each Coriolis Sickness Susceptibility Index (CSSI) test. Experimental groups were exposed for 6 hrs of autogenic feedback training to control physiological responses to motion sickness tests; control groups underwent tests without being trained.



199-20-22-10

JUL 1980

BIOFEEDBACK IN THE CONTROL OF SPACE MOTION SICKNESS

P. S. Cowings (NASA-ARC)

Patterns of individual autonomic response to motion sickness are consistent across different motion stimuli.

Learned autonomic control for suppression of motion sickness transfers across several different motion stimuli. Mass training is not as effective or permanent as distributed training.

Men and women are similar in susceptibility to motion sickness and in their ability to learn symptom control.

Future investigations will be on conditioning direct control of gastric motility, pressure, or stomach pH and on developing computer-assisted procedures for conditioning multiple autonomic parameters.

PUBLICATIONS

None

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HISTOCHEMICAL CHARACTERIZATION OF THE CNS EMETIC APPARATUS

K. R. Brizzee (Tulane University)

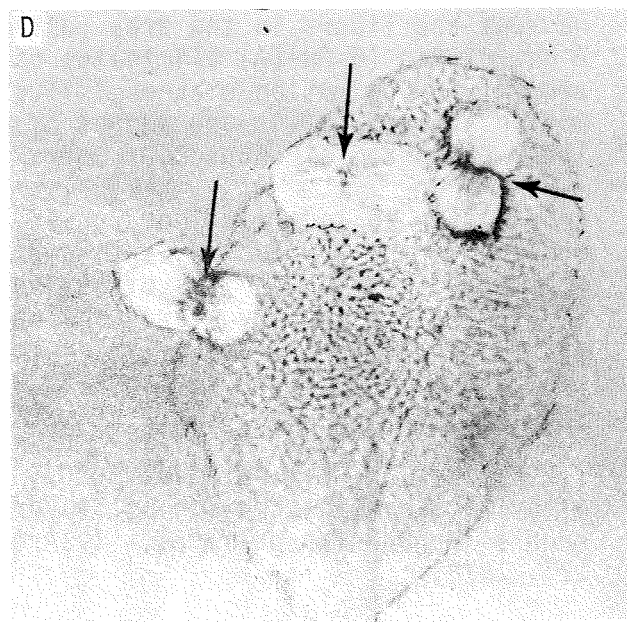
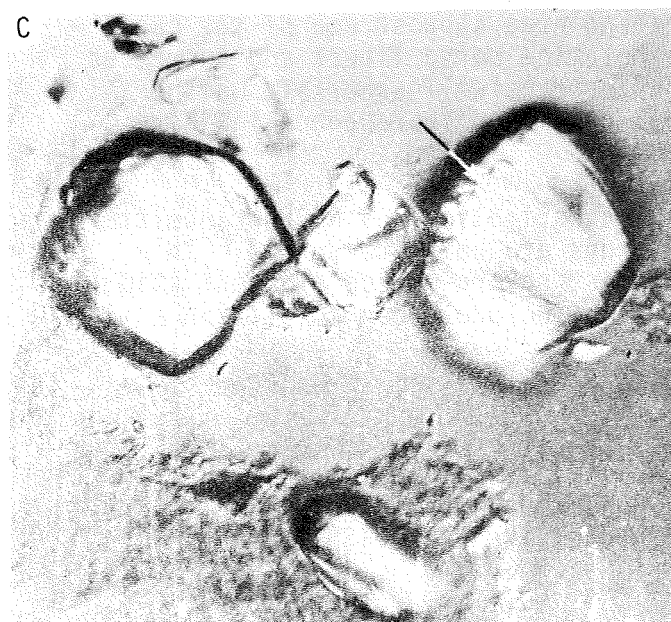
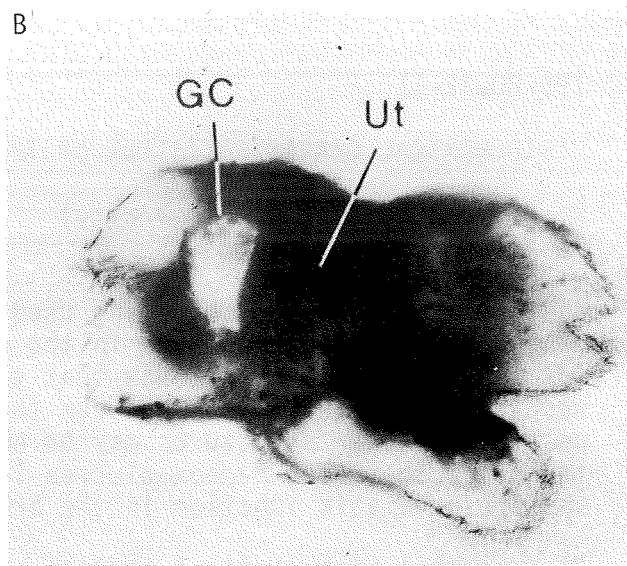
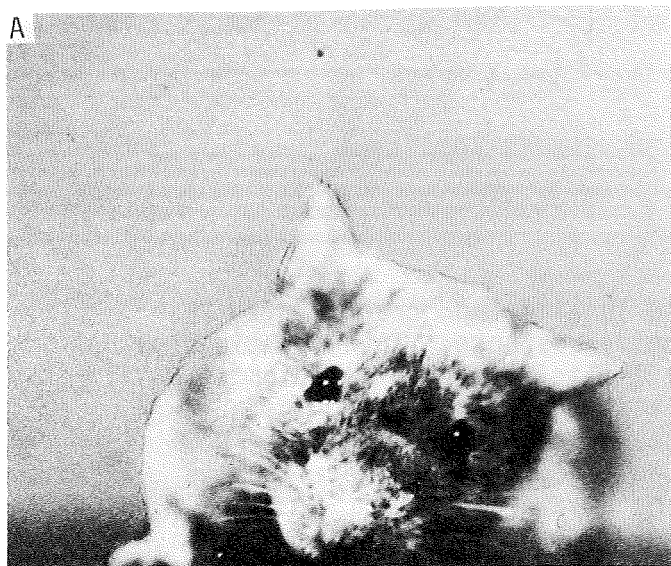
Histochemical methods are being used to localize and characterize CNS components that are involved in the emetic response. Investigations of the monkey, dog, and cat show that the emetic response to motion stimuli results from interactions between the vestibular system and the area postrema. Other structures may be necessary to the response. A new technique that uses 2-deoxyglucose is being employed to localize the vestibulo-emetic function in the brainstem.

Fluorescence histochemical studies show an abundance of catecholamine neurons and fibers in the area postrema and area subpostrema of the cat. A neurotoxin (6-OH-DA) eliminates catecholamine nerve fibers and increases sensitivity to motion sickness. Further studies will ascertain whether motion stimuli affect the amount of catecholamine fluorescence in these lower brainstem structures.

In addition to localization studies and investigations of neurotransmitters, studies of the efficacy of anti-emetic drugs are being conducted. Thiethylperazine (Torecan) is effective against severe motion sickness stimuli. Studies with other drugs are continuing and include those localizing action to the brain.

PUBLICATIONS

1. Brizzee, K. R., Palazzo, M. C., Klara, P. M., and Hofer, H. "Effects of systemic administration of 6-hydroxydopamine on the circumventricular organs in nonhuman primates. I. Area Postrema." CELL TISS RES 187:115-127, 1978.
2. Palazzo, M. C., Brizzee, K. R., Hofer, H., and Mehler, W. R. "Effects of systemic administration of 6-hydroxydopamine on the circumventricular organs in nonhuman primates. II. Subfornical Organ." CELL TISS RES 191:141-150, 1978.
3. Brizzee, K. R., Ordy, J. M., and Mehler, W. R. "Effect of ablation of area postrema on frequency and latency of motion sickness-induced emesis in the squirrel monkey." PHYSIOL BEHAV 24:849-853, 1980.



Observations of otoconia from tilted-head mouse. (A) Tilted-head mouse. (B) Surface preparation of utricle (Ut) showing giant crystal (GC), 50X. (C) Flower-petal shaped giant crystals (arrow indicates lamellation), 200X. (D) Bow-tie or butterfly shaped malformed giant otoconia with central narrowing (arrows), 125X.

ENVIRONMENTAL AND GENETIC EFFECTS OF GRAVITY RECEPTORS

D. J. Lim (Ohio State University Hospital)

The mechanisms involved in the formation and maintenance of the otoconia (also called otoliths) in the inner ear are poorly understood. The objectives of this project are: (1) to clarify these mechanisms, (2) to study morphological abnormalities in the otoconial organs due to exposure to abnormal gravitational environments, and (3) to study the behavioral and physiological abnormalities associated with observed morphological changes.

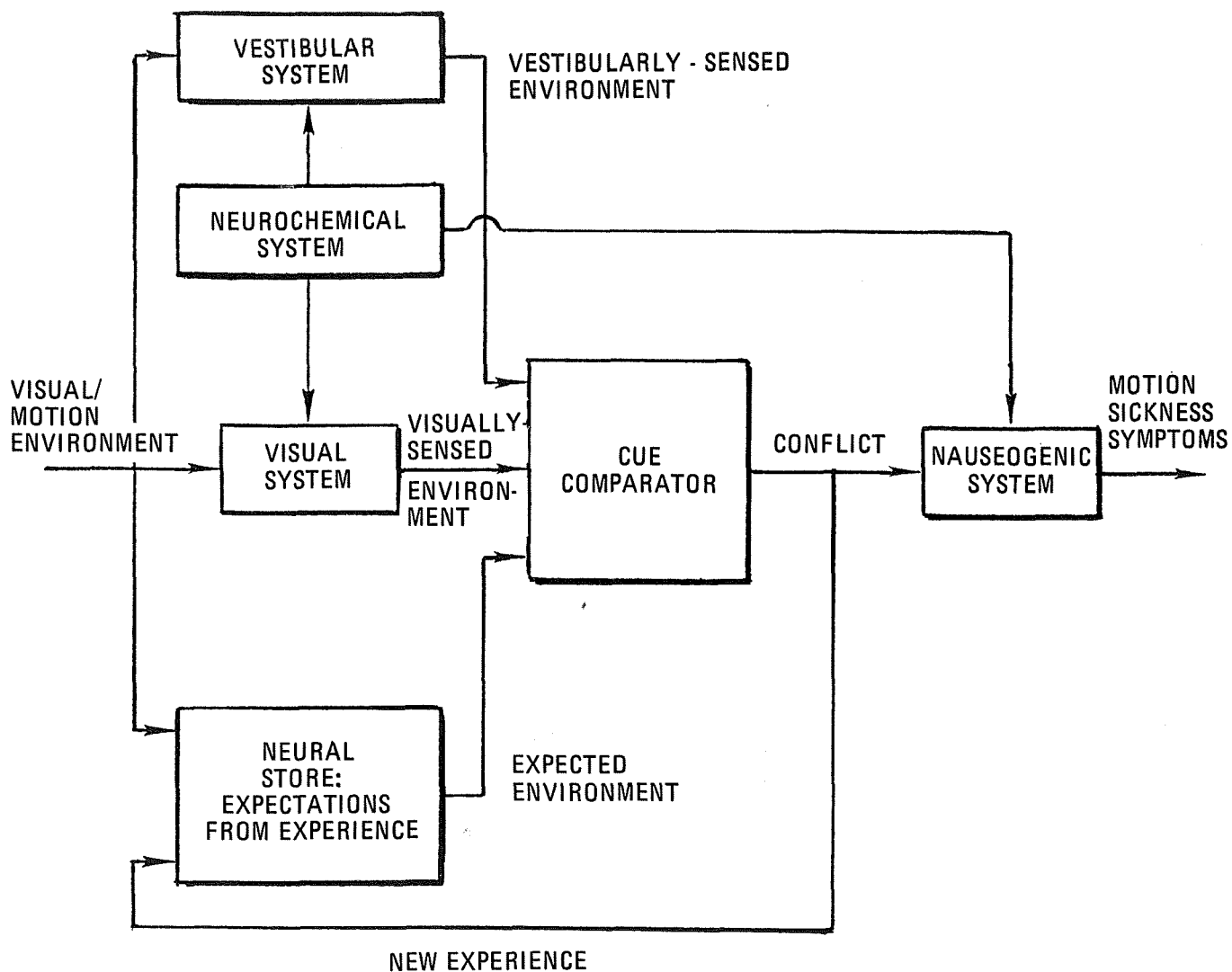
The developmental histology of the otoconial organs is studied in mice. Otoconia seeding occurs in 11-13 gestational days as small globules of organic substances which appear to be secreted by supporting cells. Young otoconia appear to have one or more nuclei, and the pointed ends of the crystals appear later. Genetically malformed otoconia appear to be formed by fusion of small crystals, as in the case of intoxication with a diuretic drug, ethacrynic acid.

The morphological study of the central area of the otoconial organs shows that the cilia in that area are free to be stimulated by the flow of endolymph and are best suited for specific detection of dynamic changes in gravitational force or body movement, since the cilia in this area are embedded into the overlying gelatinous membrane.

Reduction in the number of otoconia within tilted-head and pallid mice gravity receptors results in hypostimulation similar to that of the space environment. Behavioral studies show peripheral anomalies such as disorientation in water and inability to right during a free fall. Studies on the tilted-head mice show no behavioral anomalies until otoconia are reduced to 20%, or less, of normal. The effects of this sensory deprivation are also being examined in the vestibular brainstem.

PUBLICATIONS

1. Lim, D. J., Erway, L. C., and Clark, D. L. "Tilted-head mice with genetic otoconial anomaly: Behavioral, physiological and morphological correlates." In: Vestibular Mechanisms in Health and Disease, J. D. Hood, ed. Academic Press, London, 1978, pp 195-206.



Global structure based on conceptual sensory conflict model.
(From: Riedel, S. A. "A comprehensive system model for motion/
space sickness -- preliminary results." Proc. 16th Annual Conf.
on Manual Control, MIT, 5-7 May 1980, pp 349-68.)

199-20-22-13

NOV 1980

SYSTEMS MODEL FOR SPACE MOTION SICKNESS

H. R. Jex (Systems Technology, Inc.)

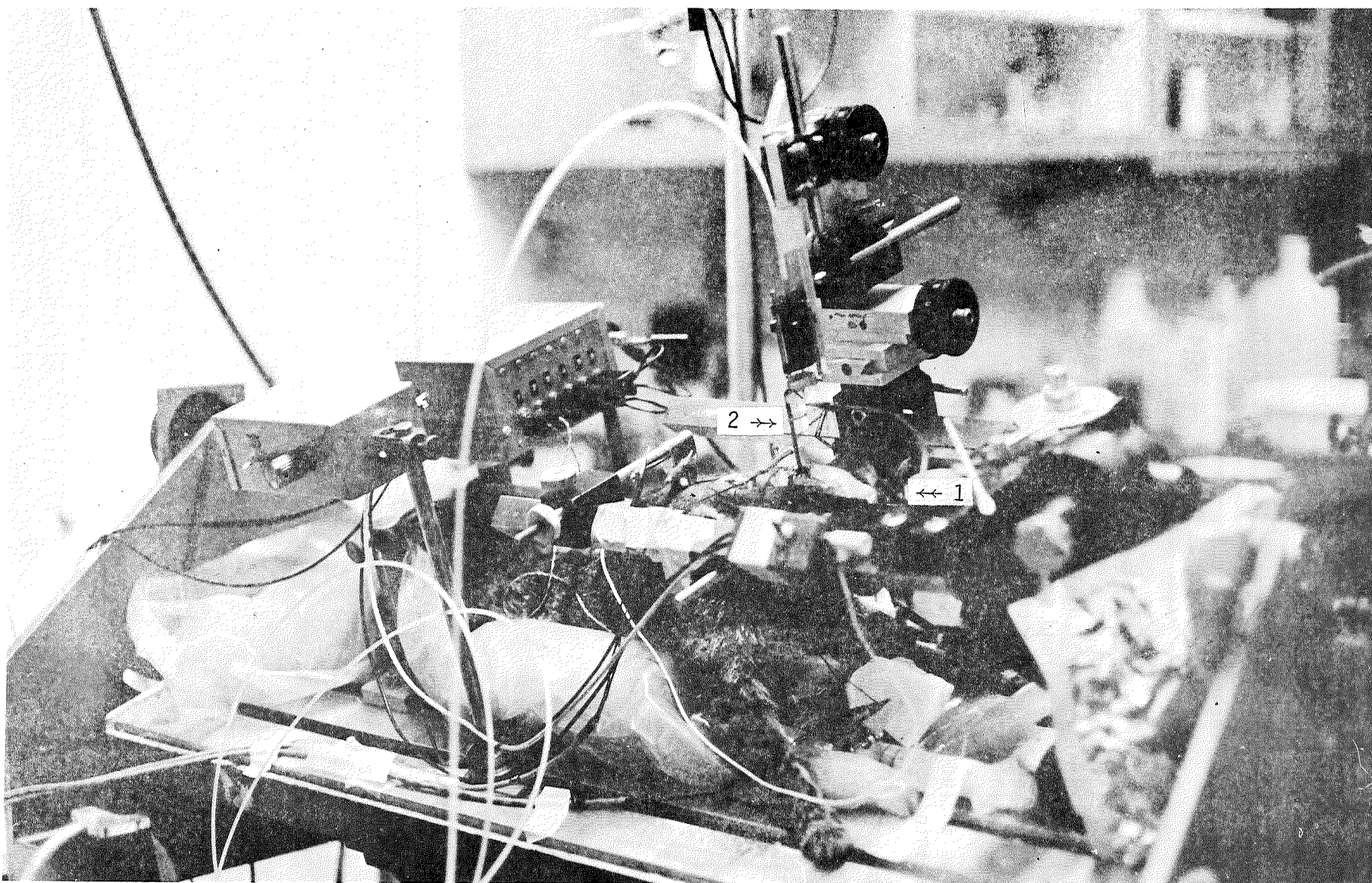
This project is the first phase in the development of a functional model for motion sickness. This mathematical model will be applicable for predicting the conditions conducive to the syndrome, screening susceptible individuals, and minimizing the likelihood and/or severity of the syndrome by altering environmental and motion parameters. Such a dynamic approach can describe the disparate mechanical and psychophysiological elements and their complex interactions.

This phase includes the review and synthesis of observations on motion sickness into a systematic data base.

Future phases will attempt to validate the model in humans and animal studies and comparatively evaluate the model's functional efficacy in both one and zero gravity.

PUBLICATIONS

None



Decerebrate cat in lateral roll-tilt experiment. The cat is partially obscured by the stereotaxic apparatus used to hold the head ($\leftrightarrow 1$) rigidly in a standard position. The animal and supporting hardware are mounted on a base plate, which in turn may be subjected to roll-tilt patterns of up to 20° about an axis through the animal's head. Here, the platform is tilted 20° toward the viewer. Muscle activity in forelimb and neck muscles is recorded using EMG electrodes sewn into the muscle. A glass micropipette electrode ($2 \leftrightarrow$) measures the activity of single brainstem neurons in the vestibular nuclei.

VESTIBULOCOLLIC REFLEXES OF OTOLITH ORIGIN

V. J. Wilson (Rockefeller University)

Physiological studies of the vestibular system and its reflexes have emphasized semicircular canals. The purpose of this project is to develop a comprehensive description of the otolith organs, their reflexes, and their role in the maintenance of body posture.

Studies of vestibulo-spinal reflexes are being conducted on cats without cerebrums which are exposed to roll-tilt stimulation. Thus far, results have indicated that the otolith system produces reflexes in response to roll-tilt in both neck and forelimb extensor muscles. At lower frequencies of tilt, the otolith organs are effective; at higher frequencies semicircular canals appear to dominate.

Work will continue along similar lines, with the added capability to record from central otolith neurons involved in these reflexes in intact and canal-plugged cats.

PUBLICATIONS

1. Wilson, V. J., Peterson, B. W., Fukushima, K., Hirai, N., and Uchino, Y. "Analysis of vestibulocollic reflexes by sinusoidal polarization of vestibular afferent fibers." J NEUROPHYSIOL 42(2):331-46, 1979.
2. Wilson, V. J. and Melvill-Jones, G. Mammalian Vestibular Physiology. Plenum Publishers, New York, NY, 1979.
3. Wilson, V. J. and Peterson, B. W. "Peripheral and central substrates of vestibulospinal reflexes." PHYSIOL REV 58:80-105, 1978.

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3. BONE DEMINERALIZATION

UPN	PI	SHORT TITLE
199-20-31-01	Schneider	Long-Term Bedrest
199-20-31-03	Neer	Hormonal Control of Calcium and Bone
199-20-31-04	Altchuler	Mechanisms of Skeletal Loss
199-20-31-09	Kamel	Bone Growth Endosseous Implants
199-20-31-10	Genant	Computer Tomography of Vertebrae
199-20-31-12	Cintron	Vitamin D/Vitamin K in Calcium Control
199-20-31-13	Arnaud	Calcium Regulating Hormones
199-20-32-01	Young	Bone Metabolism and Biomechanics
199-20-32-02	Steele	Bone Elasticity
199-20-32-03	Mazess	Body Composition by Photon Absorptiometry
199-20-32-06	Holton	Calcium Homeostasis
199-20-32-07	Oyama	Hypergravity Effects of Musculoskeletal System
199-20-32-14	Kenny	Pharmacological Prevention of Bone Loss
199-20-32-15	Callahan	Radioimmunoassay for Osteocalcin

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INTRODUCTION

Progressive decrements in skeletal mass may constitute a major medical hazard in long-term spaceflight. X-ray densitometry and calcium balance studies from Gemini, Apollo, and Skylab missions show that weight-bearing bones are particularly susceptible to mineral loss: Losses from the radius and ulna were immeasurable, whereas losses from the os calcis, or heel bone, were as high as 7.9% of mineral content.

In spaceflight, the degree of bone loss from the os calcis seems to correlate with the degree of negative calcium balance, which persists throughout spaceflight. The high calcium loss is accompanied by losses in nitrogen, phosphate, potassium, and muscle mass. Extrapolation of this data to six months of weightlessness results in a loss of 2.5 - 3.0% of the total body calcium.

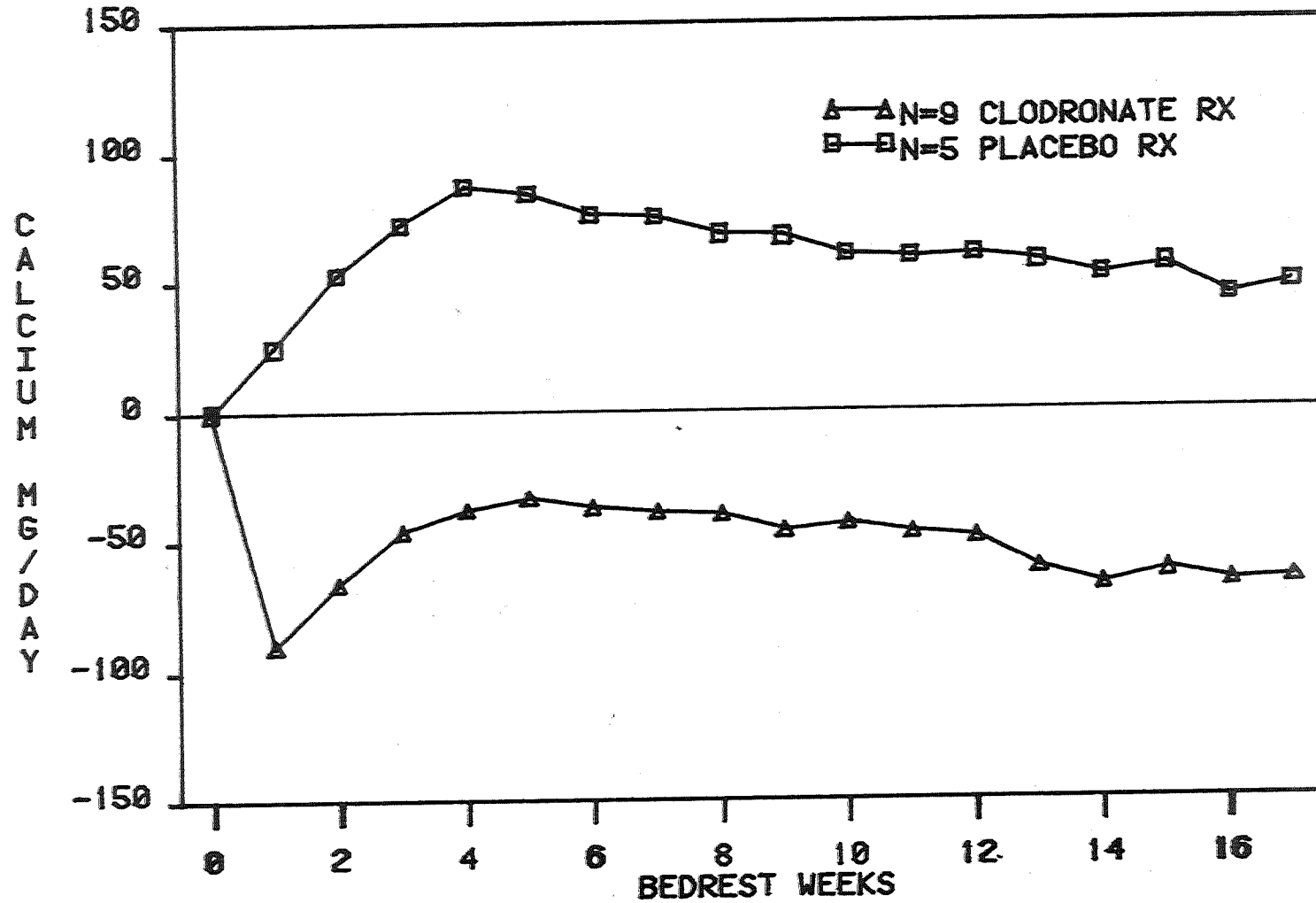
Just how extensive the losses will be during long-term spaceflight is not known. The point at which these losses become irreversible is also unknown. Extensive losses in skeletal mass may lead to kidney stones and increased potential for fractures, among other dangers.

One of the main objectives of this RTOP is to determine the mechanism of bone demineralization. That the rate of bone resorption exceeds the rate of bone formation in the absence of normal gravitational stress is a possible starting point. Underlying mechanisms are being investigated in ground-based experiments using human and animal subjects during bedrest or other forms of immobilization. These include studies on bone density, calcium kinetics, and hormonal control (e.g., parathyroid hormone, calcitonin, and vitamin D metabolites). Noninvasive methods of measuring skeletal status are being developed as necessary.

Countermeasures to prevent and treat alterations are also being tested. Current areas include controlled diet, exercise, and hormone treatment. To date, neither dietary supplementation with phosphate or calcium, nor static or dynamic impact loading of the skeletal system, nor isotonic exercises have prevented bedrest-induced bone loss in man.

URINARY CALCIUM CHANGE FROM BASELINE

Schneider
31-01



The graph depicts the beneficial effect of clodronate (Proctor & Gamble Co.) as compared to placebo on urinary calcium in 14 healthy male bedrest volunteers.

ATTEMPTS TO PREVENT BONE MINERAL LOSS DURING PROLONGED BEDREST

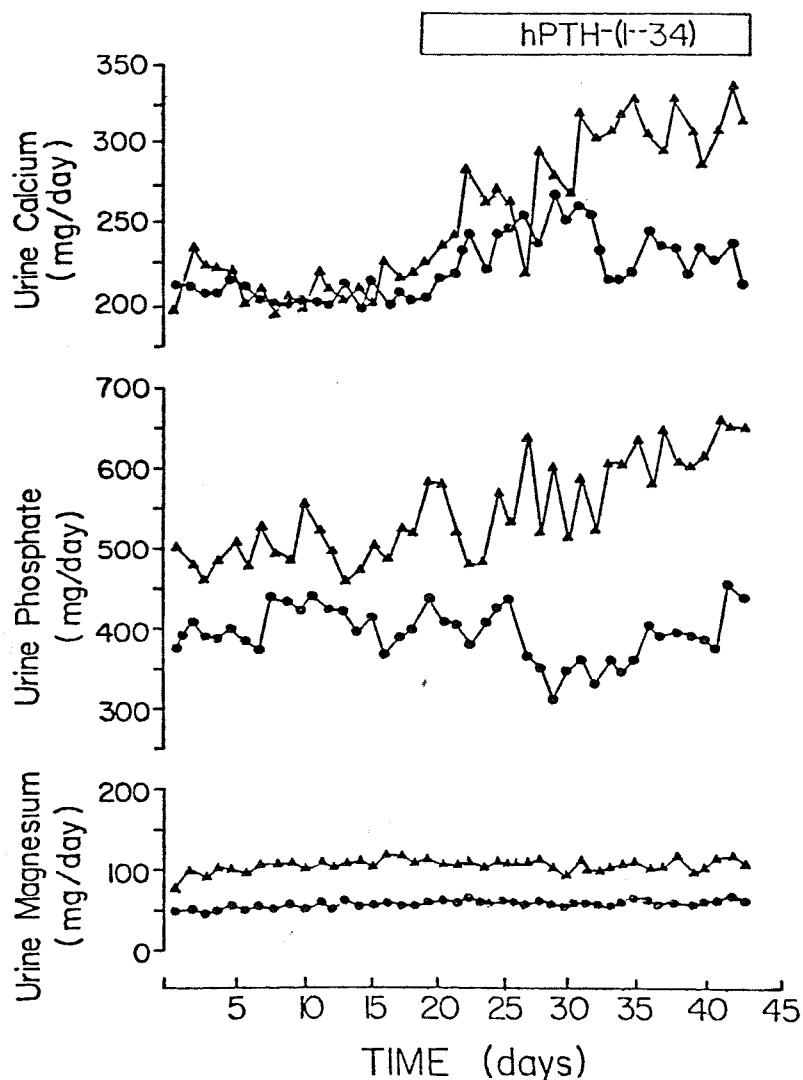
V. S. Schneider (USPHS Hospital, San Francisco)

Both weightlessness and prolonged bedrest are accompanied by increased calcium in the urine as bone mineral is lost. The immediate rise in urinary calcium continues to increase for six weeks before a plateau is reached. Bone breakdown, as measured by the urinary output of hydroxyproline, an amino acid by-product of the bone matrix, also occurs during the first week of bedrest and reaches a maximum during the sixth week. There is little information on the extent of bone mineral loss to be expected with repeated exposure to weightlessness or bedrest.

In order to allay any detrimental effects of weightlessness, a variety of therapeutic approaches are being taken. One method of preventing bone mineral loss uses the drug clodronate, a diphosphonate. When evaluated in nine healthy bedrest volunteers, urinary calcium did not increase in clodronate-treated subjects; seven of the nine did not lose any calcaneal mineral as measured by the bone densitometer. Clodronate presents a counter-measure sufficiently promising to be evaluated further.

PUBLICATIONS

1. Schneider, V. S., McDonald, J., Rambaut, P., et al. "Prevention of disuse osteoporosis: Clodronate therapy." Program of the 15th Annual Professional Association Meeting of the USPHS, 44, 1980.
2. Schneider, V. S., Robin, A., Vogel, J. M., and Rambaut, P. "Trabecular bone densitometry: NASA developed bone mineral analyzers." Program of the 15th Annual Professional Association Meeting of the USPHS, 44, 1980.
3. Robin, A. and Schneider, V. S. "The effect of exercise on bone mineral density." Program of the 15th Annual Professional Association Meeting of the USPHS, 44, 1980.



Mean daily urinary excretion of calcium, phosphate, and magnesium in patients given low and high doses of hPTH-(1--34). Immediately following an 18-day control period, subcutaneous injections of hPTH-(1--34) were administered each day at 6 AM, as indicated by the bar at the top of the figure. ●—● represents the low dose; ▲—▲ the higher dose.

INVESTIGATIONS IN HORMONAL CONTROL OF CALCIUM AND BONE METABOLISM

R. M. Neer (Massachusetts General Hospital)

Most ground-based investigations of bone resorption utilize prolonged bedrest for a space analog. This has been expensive and time consuming. A more efficient method of safely increasing bone resorption for a controlled period of time has recently been developed. It involves daily subcutaneous injections of a portion of synthetic human parathyroid hormone for three or four weeks. Using this analog, various countermeasures can be tested.

The loss of bone and bone calcium during spaceflight may be caused in part by excessive adrenal secretion of cortisone. Urinary secretion of free cortisol increases 1.5 - 2 fold in flight.

Exogenous cortisone, given in doses mimicking its increased endogenous secretion during spaceflight, will be used to study bone changes and whether drugs will prevent these changes.

PUBLICATIONS

1. Slovik, D. M., Neer, R. M., Ohman, J. L., Lowell, F. C., Clark, M. B., Segre, G. V., and Potts, J. T., Jr. "Parathyroid hormone and 25-hydroxyvitamin D levels in glucocorticoid-treated patients." CLIN ENDOCRIN 12:243-48, 1980.

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MECHANISMS OF SKELETAL DETERIORATION

S. I. Altchuler (NASA-JSC)

The overall negative calcium balance and the osteoporotic changes in normally weight-bearing long-bones are reversible upon return to Earth, but complete compensation for the losses is yet uncertain.

Animals flown onboard satellites exhibit a cessation of bone apposition (or formation) and a continuation, at a decreased level, of bone resorption. The ingestion of high-protein diets, such as those offered in current space missions, cause increased urinary calcium excretion (hypercalciuria) in both man and animals.

This research effort will study the interactions of dietary protein and a disuse model of spaceflight osteoporosis in animals. Animals will be fed a semi-synthetic diet of known composition, while being maintained in metabolic balance. Whole-body calcium status will be determined longitudinally, and bone histomorphometry will be studied.

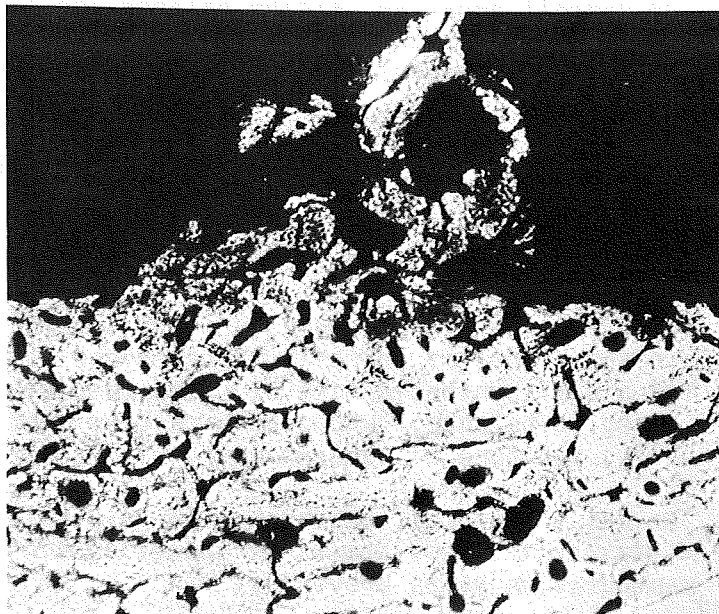
The results of this research will help determine whether dietary changes aggravate the development of spaceflight osteoporosis and whether dietary manipulation helps prevent it.

PUBLICATIONS

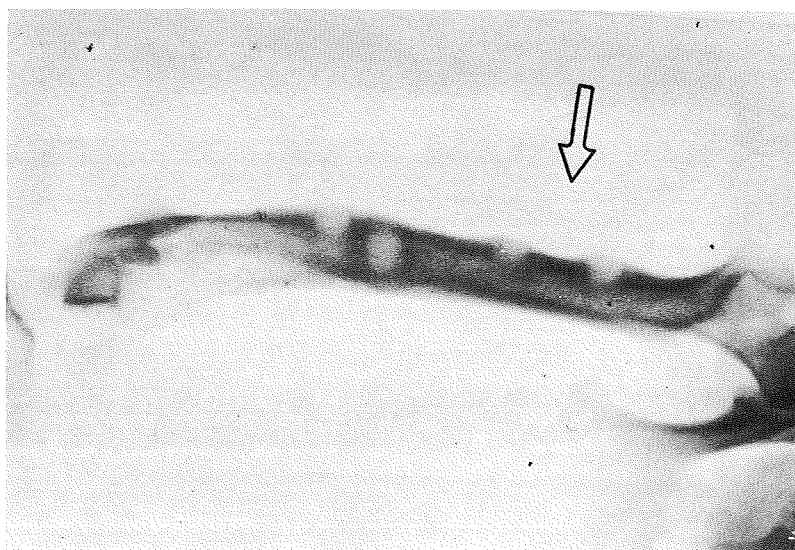
None



Implanted composite. Porous and hydrophilic in nature, the implant is composed of a crosslinked polyacrylic matrix, reinforced with alumina particles. The degree of biocompatibility of the implant in vivo is very critical to the tissue response.



Bone-implant interface. Bone cells are in direct contact with and extend into the porous implant wall. No fibrous tissue formation or other signs of rejection have been found in any of this type of composite implant to date.



Four femoral implants. Notable bone activity has taken place 6 wks post-operatively. Electron microprobe analysis will be used to compare the degree of mineralization induced by the various implants at the end of each implant period.

BONE GROWTH AND ALTERATION VIA ENDOSSEOUS IMPLANTS

I. L. Kamel (Drexel University)

This task investigates the degree of bone formation due to stress-induced physiological changes. The novel approach introduced by this project induces a stress field using a swelling endosseous implant, which allows the control of stress level and rate of application.

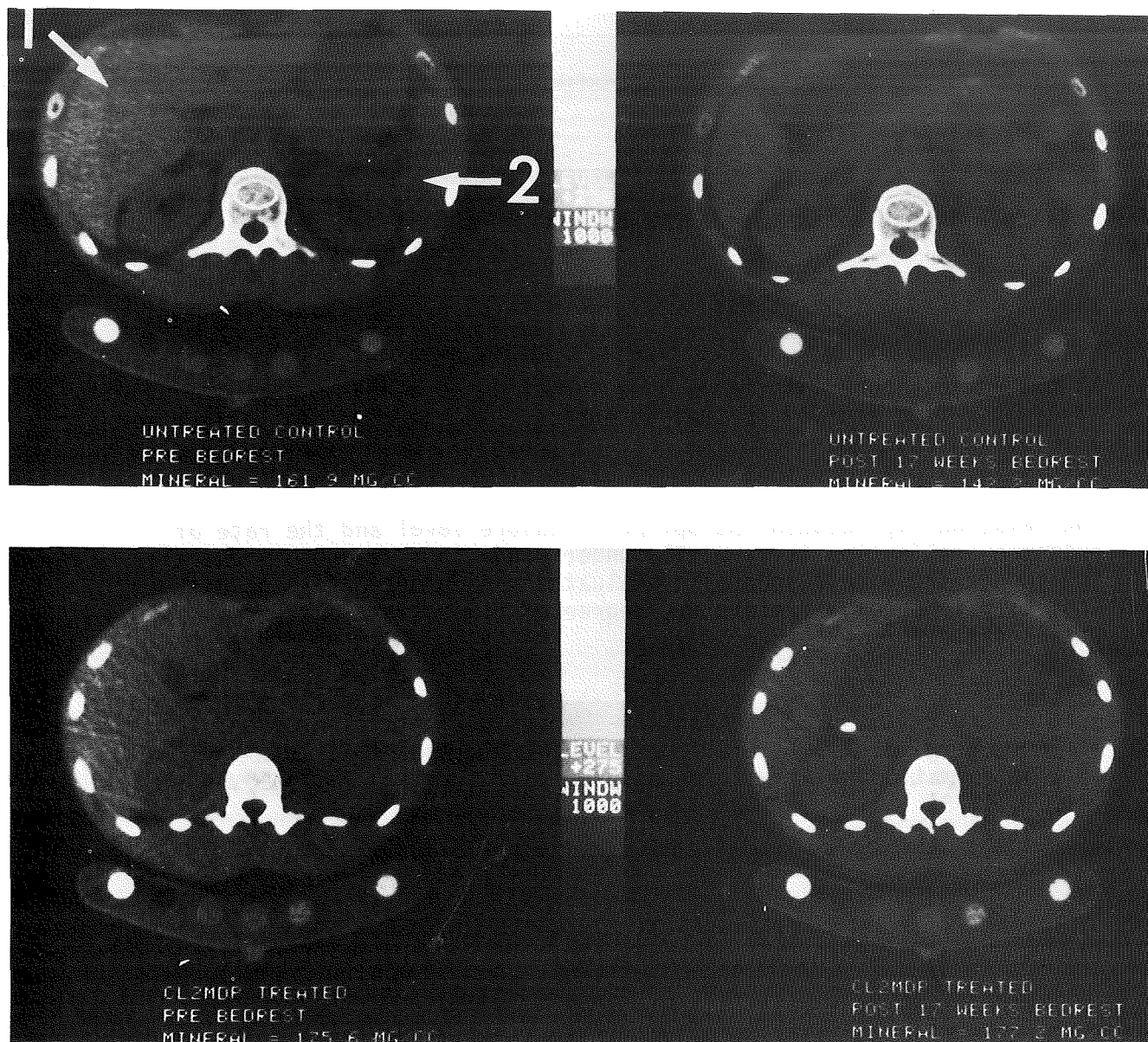
This procedure has been successful in the stimulation of bone formation at the implant-bone interface; bone formation accelerates when the proper stress level is applied to that interface. Recent findings through animal studies indicate that both the rate of pressure application and the final stress level are important to bone stimulation.

The relationship between the optimum pressure level and the rate of pressure application is currently under study in a series of femoral implants. The bone response is evaluated radiographically and histologically in order to relate the degree of mineralization to the applied stress field.

PUBLICATIONS

1. Greenberg, A. R., Kamel, I. L., Dubin, S., and Miller, A. "Stimulation of bone formation by a swelling endosseous implant." J BIOMED MAT RES 12:929, 1978.

Genant
31-10



Computed tomography (CT) scans of two subjects at the level of the first lumbar vertebra (L1) before and after 17 wks of bedrest. A series of 18-20 scans through L1 and L2 are used to obtain quantitative information shown on the figure. Elliptical region of interest defines a 4 cm³ volume element used for mineral analysis. Top: Untreated control subject who lost 12.5% of spinal cancellous mineral in the 17 wks of bedrest. Bottom: Subject treated with dichloromethyldiphosphonate (clodronate) showed no significant change in vertebral mineral content during bedrest. The streak artifacts in the lower images are due to the very low X-ray dose used in these studies. Note also the position of the liver (1) and spleen (2), which have shifted higher in the body.

QUANTIFICATION OF BONE MINERAL BY COMPUTED TOMOGRAPHY

H. K. Genant (University of California School of Medicine)

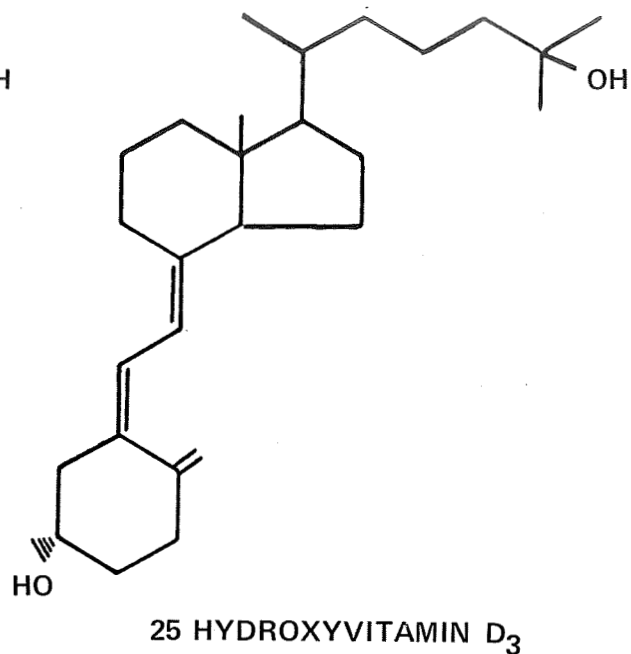
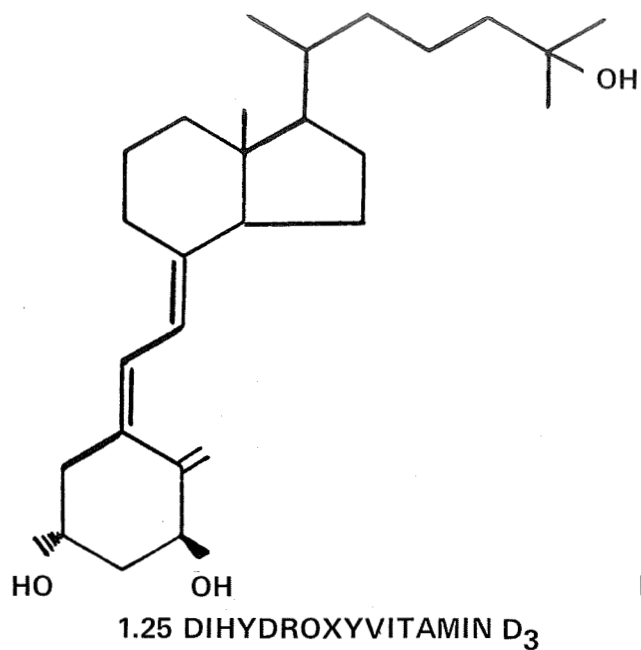
Cancellous bone comprises only 25% of total bone volume, but accounts for 50% of total bone turnover. The project focuses on the determination of cancellous vertebral mineral content. A quantitative computed tomographic (QCT) technique has been developed for this purpose.

The QCT technique adequately detected vertebral mineral loss in untreated male subjects after 17 weeks of bedrest. In vivo precision for this technique is 1.5%, and spinal mineral changes of 3-4% are detectable. The sensitivity of the system allows precise monitoring of treatment to determine the effectiveness of drug or exercise therapy.

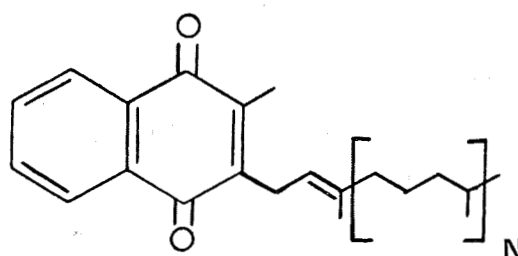
PUBLICATIONS

1. Cann, C. E. and Genant, H. K. "Models of immobilization osteoporosis and applications of quantitative bone mineral analysis." Symposium on Models and Techniques in Radiological Research, Tucson, Arizona, 1980.
2. Cann, C. E., Genant, H. K., Ettinger, B., Kolb, F. O., Gordan, G. S., and Arnaud, C. D. "Spinal mineral by computed tomography-comparison with peripheral mineral in patients and controls." Second Annual Meeting, American Society for Bone and Mineral Research, Washington, D.C., 1980.
3. Genant, H. K., Cann, C. E., Ettinger, B., and Gordan, G. S. "Bone mineral determination in the axial and appendicular skeleton." (Abstract) The Endocrine Society Annual Meeting, Washington, D.C., 1980.

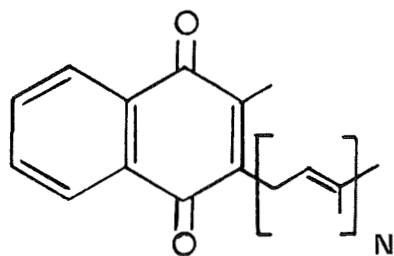
STRUCTURES OF KEY VITAMIN D METABOLITES



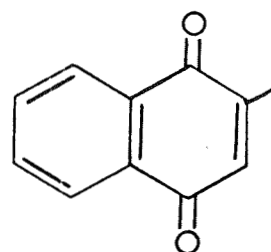
STRUCTURES OF THE K VITAMINS



VITAMIN K₁
(N=3; PHYLLUQUINONE)



VITAMIN K₂
(MENAQUINONE SERIES)



VITAMIN K₃
(MENADIONE)

199-20-31-12

OCT 1980

VITAMIN K- AND VITAMIN D-DEPENDENT REGULATORY MECHANISMS IN CALCIUM HOMEOSTASIS

N. M. Cintrón (NASA-JSC)

Normal calcium balance is regulated by the coordinated molecular action of a variety of biochemical agents, among which two emerge as being particularly important: (1) the vitamin D-derived metabolites and (2) the recently discovered vitamin K-dependent, calcium binding proteins (CaBPs) of bone and kidney. A thorough understanding of their mechanisms of action at the cellular and biochemical levels in the maintenance of this critical calcium homeostasis is far from complete. Therefore, efforts are being directed toward studying the molecular basis of both vitamin D and vitamin K metabolism as it relates to the maintenance of calcium homeostasis, normally and in space.

One major objective is the quantitative analysis of selected vitamin D metabolites and of free and protein-bound γ -carboxyglutamate (vitamin K-dependent) residues in plasma and urine samples from spaceflight crews and bedrest subjects. The necessary procedures and assays have been developed and tested. Altered levels of these metabolites reflect mineral imbalances and provide not only functional information, but therapeutic and diagnostic information as well.

Another focus of research is the role of the vitamin K-dependent CaBPs of kidney in the renal handling and metabolism of calcium. This involves the purification, localization, and characterization of the CaBPs of chick kidney using standard biochemical techniques and assays.

PUBLICATIONS

None

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DETERMINATION OF CALCIUM REGULATING HORMONES IN PROLONGED BEDREST AND SPACE TRAVEL

C. D. Arnaud (Fort Miley VA Hospital)

Levels of calcium regulating hormones were determined in 14 young, healthy male volunteers during ten weeks of control (ambulation) and 17 weeks of bedrest. Nine other subjects were observed during three weeks of ambulation, six weeks of ambulation with treatment, and 14 weeks of bedrest with treatment. Subjects were treated with clodronate, which has been shown to inhibit bone loss in several animal experiments.

Parathyroid hormone, vitamin D, and calcitonin were measured weekly. Blood was drawn every four hours at three different points during the study (once during untreated ambulation, twice during bedrest weeks 5 and 15) to determine diurnal changes in these hormones.

The results of these studies are currently being analyzed.

PUBLICATIONS

None

Young
32-01



Tomograph of cross-section of proximal left tibia of control animal. Anterior tibia is shown on the right; the smaller fibula is shown below and to the left.

BONE METABOLISM AND BIOMECHANICS

D. R. Young (NASA-ARC)

Various methods have been used to evaluate bone mineral loss in a restrained monkey. Studies using photon absorptiometry, radiography and X- and gamma-ray computer tomography showed that immobilized monkeys lost 10-22% of bone mineral from the tibia and lumbar vertebrae within three to six months. It took eight months of recovery and rehabilitation to replace tibial mineral content and strength. Neither electrical stimulation of the bone nor high calcium diet prevented bone demineralization during the immobilized period.

The mechanisms underlying this mineral loss are yet unclear. Calcium kinetic studies demonstrate a large increase in bone turnover and resorption rates during immobilization, indicating that factors promoting the synthesis and destruction of bone tissue are involved. The pH of blood becomes more basic during immobilization, indicating a disruption of the bone buffer system. Future research will focus on the role of parathyroid hormone and aldosterone in acid-base status.

PUBLICATIONS

1. Cann, C. E., Genant, H. K., and Young, D. R. "Comparison of vertebral and peripheral mineral losses in disuse osteoporosis in monkeys." *RADIOLOGY* 134:525-529, 1980.
2. Young, D. R., Howard, W. H., Cann, C. E., and Steele, C. R. "Noninvasive measures of bone bending rigidity in the monkey (*M. nemestrina*).¹" *CALC TISS INTL* 27:109-15, 1979.
3. Young, D. R. "Radiographic evidence of disuse osteoporosis in the monkey (*M. nemestrina*).²" *PHYSIOLOGIST* 22(5):108, 1979.



Subject with arm in position to be measured by SOBSA (see text).

BONE ELASTICITY

C. R. Steele (Stanford University School of Engineering)

A microprocessor controlled device has been developed that can measure noninvasively the gross bending stiffness of bones. This device (called SOBSA) is portable and can collect and analyze data on one bone in seconds (previous methods require hours).

The ulnas of about 300 human subjects have been measured. Also measured were ulnas and tibias in two monkeys subjected to six months of confinement and in a control monkey. Correlation between bone stiffness and mineral content was excellent.

Several inadequacies of the prototype device are apparent: high sensitivity to interference from other equipment, large error in the data analysis algorithm, and a high variability among operators in positioning of the subjects. Future plans include the development of SOBSA-2 specifically for testing monkeys and SOBSA-3 for humans, both without the deficiencies of SOBSA-1.

PUBLICATIONS

None

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PHOTON ABSORPTIOMETRIC METHODS FOR MEASURES OF BODY COMPOSITION

R. B. Mazess (University of Wisconsin)

Photon absorptiometric techniques have been developed to measure mineral content in bone and fluid accumulation in soft tissue. The technique has exhibited errors in precision and in accuracy of less than 2%. Special instrumentation allows direct measurement of the lumbar spine and femoral neck. This type of scanner will aid in diagnosis and monitoring of bone changes with disease, immobilization, and therapy.

Total body bone scans were developed and evaluated in normal subjects and patients. These scans measure not only total body calcium at very low doses of radiation (< 1 mrem), but bone mineral and body composition in all body areas as well.

Precision in measurements, particularly for femoral neck determinations, will be improved. Future studies will also examine the contribution of absorptiometry to conventional nuclear medicine bone scans in order to allow better localization and correction of emission scan data.

PUBLICATIONS

1. Mazess, R. B. "Measurement of skeletal status by noninvasive methods." CALC TIS INTERN 28:89-92, 1979.
2. Mischler, D. H., Chesney, J., Chesney, R. W., and Mazess, R. B. "Demineralization in cystic fibrosis detected by direct photon absorptiometry." AM J DIS CHILD 133:632-35, 1979.
3. Barden, H. S., Mazess, R. B., Rose, P. G., and McAweeney, W. "Bone mineral status by direct photon absorptiometry in institutionalized adults receiving long-term anticonvulsant therapy and multivitamin supplementation." CALC TIS INTERN 31:117-21, 1980.

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CALCIUM HOMEOSTASIS IN ALTERED GRAVITY

E. M. Holton (NASA-ARC)

In addition to fluid shifts and decreased loading on bones, alterations in hormonal levels, blood flow, and neural input may also contribute to the changes in calcium metabolism observed during spaceflight. This effort focuses on elucidating the mechanisms involved and the level of organization required (cell, organ, or whole animal).

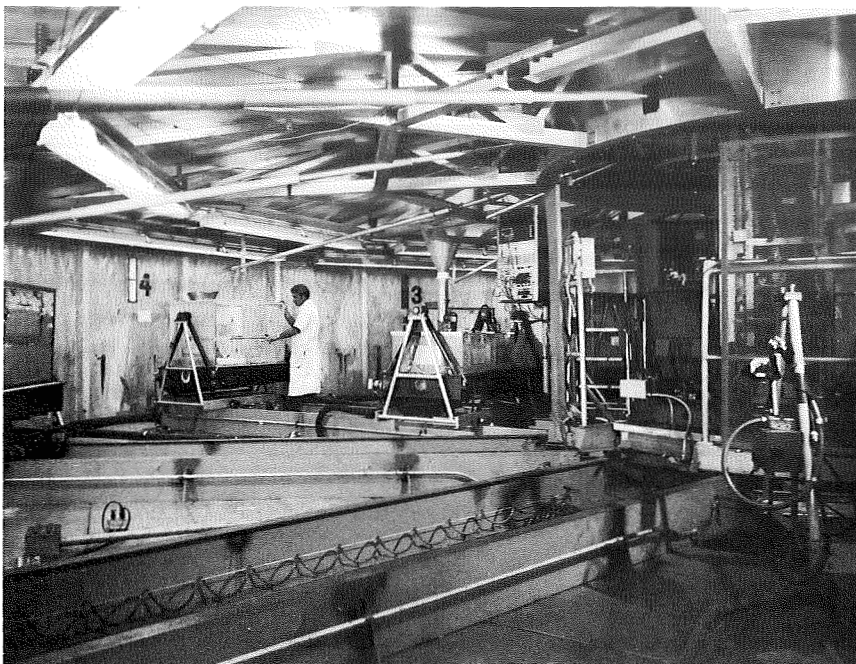
Experimental evidence shows that bone cells have $1,25-(OH)_2D_3$ receptors. This implicates the involvement of the active metabolite of Vitamin D in bone metabolism.

A protein that inhibits bone formation has been found to be produced by bone in organ culture. Further characterization of the protein and the determination of its physiological role may be significant in the elucidation of mechanisms of bone demineralization in spaceflight.

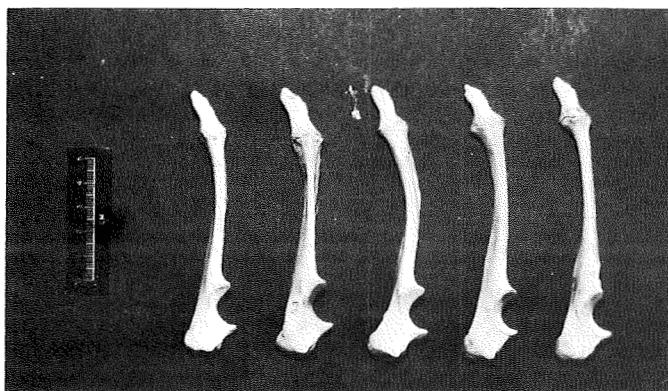
Future studies will further define the effects of hormones in isolated bone cells, primarily osteoblast-like cells.

PUBLICATIONS

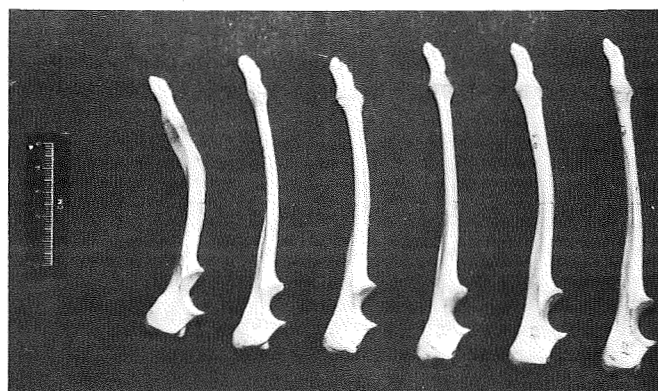
None



Interior view of 52-ft diameter centrifuge. Swivel-mounted cages can be at any position at the end of any one of the ten radial tracks. Copper shielded cages are used for biotelemetry measurements (heart rate, temperature) and smaller cages for smaller animals (rats, mice). Feeding and waste removal of animals are accounted for. Animals can be viewed from the stationary platform (on right) or from remote control television.



CENTRIFUGED DOGS



CONTROL DOGS

Ulna bones of chronically centrifuged male beagles (6 mos, 2.5 G) versus controls. Centrifuged bones are significantly shorter and their cross-sections thicker (26% increased mean sagittal diameter) than control bones.

HYPER- AND HYPOGRAVITY EFFECTS ON MUSCULOSKELETAL SYSTEM OF DOGS

J. Oyama (NASA-ARC)

Through ground-based centrifuge studies, effects of both increased and decreased gravitational force on bone growth, development, and remodeling are under investigation. The findings should help elucidate mechanisms of bone demineralization during prolonged spaceflight and assess the use of the centrifuge as a countermeasure.

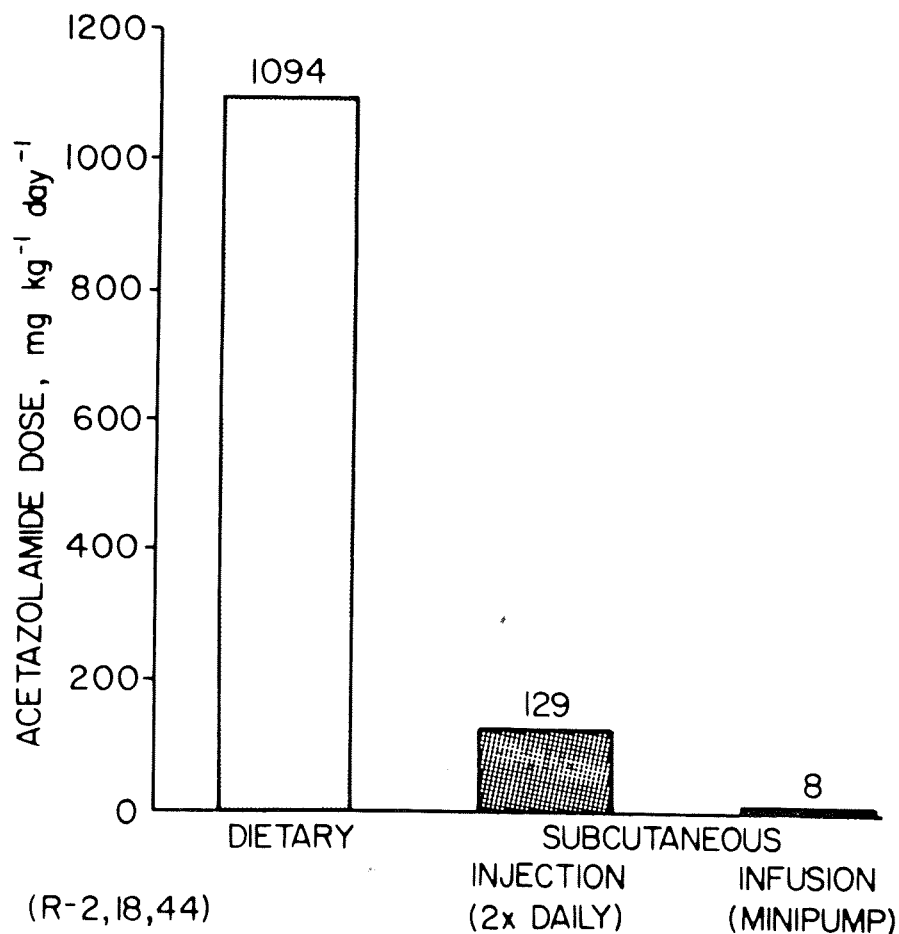
Blood of chronically centrifuged (2.5G) beagle dogs has been analyzed for the response of various bone-related hormones to hypergravity. These dogs have been centrifuged for up to one year.

Tetracycline and photon absorptiometry measurements on bones from 3-month, hypergravity-adapted young dogs are near completion.

PUBLICATIONS

1. Morgan, J. P., Fisher, G. L., McNeill, K. L., and Oyama, J. "Abnormal canine bone development associated with hypergravity exposure." AM J VET RES 40:346, 1979.
2. Oyama, J., Daligcon, B. C., Chan, L. Q., and Keil, L. C. "Hormonal blood glucose, lactate, and hematologic changes in young beagle dogs during hyper-G stress exposures and adaptation to chronic centrifugation." PHYSIOLOGIST 22:67, 1979.
3. Doden, E., Oyama, J., and Amtmann, E. "Effect of chronic centrifugation on bone density of dog." ANAT EMBRYO 153(3):321-9, 1978.

PREVENTION OF DISUSE ATROPHY OF BONE IN RATS
DIETARY VERSUS SUBCUTANEOUS ACETAZOLAMIDE
EFFECTIVE DOSES



Effectiveness of anti-bone loss drug as altered by mode of administration. Acetazolamide decreases denervation-induced bone loss in rats, but its effectiveness is dependent on its mode of administration. As can be seen from the graph, subcutaneous infusion using the osmotic minipump is the most effective, requiring only 8 mg/kg/d.

PHARMACOLOGICAL PREVENTION OF BONE LOSS

A. D. Kenny (Texas Tech Health Sciences Center School of Medicine)

Studies in the rat demonstrated that the carbonic anhydrase inhibitory drug, acetazolamide, not only blocks parathyroid hormone-induced bone resorption but also prevents the development of disuse osteoporosis. This task extends these investigations to explore more fully the potential usefulness of acetazolamide and related drugs for the prevention of calcium loss.

Acetazolamide effectively decreases denervation-induced bone loss in rats when administered by continuous subcutaneous injection using the osmotic minipump. The incorporation of a buffer (THAM) in the acetazolamide solution enhances the effectiveness of the drug. When administered at doses effective in reducing bone loss but much less than normal therapeutic levels, acetazolamide has no significant effect on blood acid-base balance.

Benzolamide, another carbonic anhydrase inhibitor, is in some respects less harmful than acetazolamide but is also less effective in preventing bone loss.

Further work will be done to test the effectiveness of combining acetazolamide with benzolamide and other agents known to prevent bone loss to uncover a therapeutic combination of drugs which may be administered at doses that minimize side effects.

PUBLICATIONS

1. Kenny, A. D. "Protective effect of parenteral acetazolamide in a rat model of disuse atrophy of bone." PHARMACOLOGIST 20:152, 1978.
2. Kenny, A. D., Yee, J. A., and Lutherer, L. O. "Inhibition of disuse atrophy of bone in rats by continuous subcutaneous infusion of acetazolamide." CALC TISSUE INT 28:157, 1979.

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A RAPID, SENSITIVE, SELECTIVE RADIOIMMUNOASSAY FOR OSTEOCALCIN

P. X. Callahan (NASA-ARC)

Analytical methods for osteocalcin are heavily dependent on detection of its component amino acid, γ -carboxyglutamic acid. Previous methods have been tedious and difficult. An efficient radioimmunoassay has been developed which is capable of detecting very low levels of osteocalcin while maintaining reproducibility.

This assay has been used to demonstrate a ten-fold increase in circulating osteocalcin in rats from one day before birth to a peak at ten days of age, and has demonstrated that serum levels respond in direct proportion to weight gain in hypophysectomized rats that have been supplemented with growth hormone. It has also determined that certain (probably damaged) γ -carboxyglutamic acid-containing proteins are not osteocalcin.

Work is in progress on gross and microscopic antibody localization of osteocalcin in bone specimens, including work on: the effects of various drugs on osteoporosis in man in relation to the levels of osteocalcin in bone and blood; the effects of hormones on osteocalcin in relation to the normal calcification process; and the microscopic localization of osteocalcin within bone by immunochemistry.

PUBLICATIONS

None

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4. MUSCLE ATROPHY

UPN	PI	SHORT TITLE
199-20-41-05	Booth	Antigravity Muscle Fiber Alterations
199-20-41-07	Fitts	Skeletal Muscle Alterations with Disuse
199-20-42-01	Ellis	Proteolysis in Muscle Atrophy
199-20-42-02	Ellis	Growth Factors in Muscle Atrophy
199-20-42-03	Grindeland	Growth Hormone in Protein Balance
199-20-42-04	Ginoza	Protein Turnover in Atrophy and Hypertrophy

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INTRODUCTION

The decrease in calf girth during spaceflight is not only due to headward fluid shifts, but to muscle breakdown as well; Skylab and Cosmos spaceflights indicated significant atrophy of skeletal muscles. Data on human subjects from 28- and 56-day Skylab flights indicated a 25% loss in leg strength and volume. In the 84-day Skylab flight, treadmill exercise was employed and only a 7-8% loss was found, although the reduction was hardly sufficient, and negative nitrogen balance persisted.

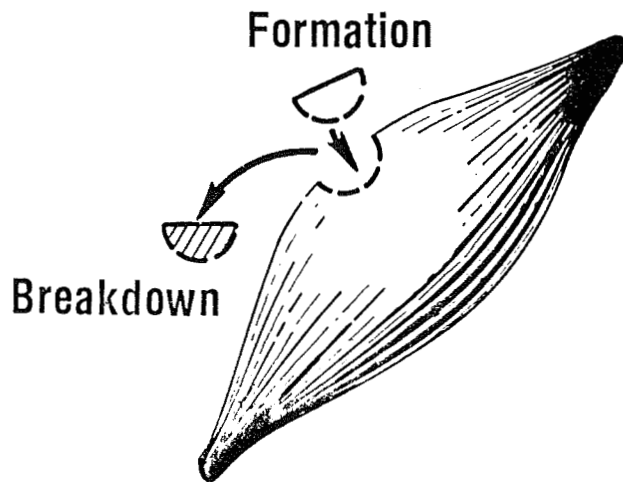
The overall aims of this research program are to determine the underlying causes of the atrophy observed in the skeletal muscle of both humans and animals during spaceflight and to develop suitable measures to counter these undesirable changes. Specific objectives are to develop and validate methods for monitoring the rate of atrophy, to conduct basic research on biochemical and physiological mechanisms which regulate muscle mass and function, and to investigate possible countermeasures.

The role of physical activity and gravitational force in the maintenance of muscle mass and function is investigated, as is the role of muscle innervation and hormones. As with bone demineralization during weightlessness, whether muscle wasting is a result of decreased formation or increased breakdown is the subject of much research. The antigravity muscles (e.g., soleus muscle) seem to be more affected than other muscles and are thus the usual object of these investigations.

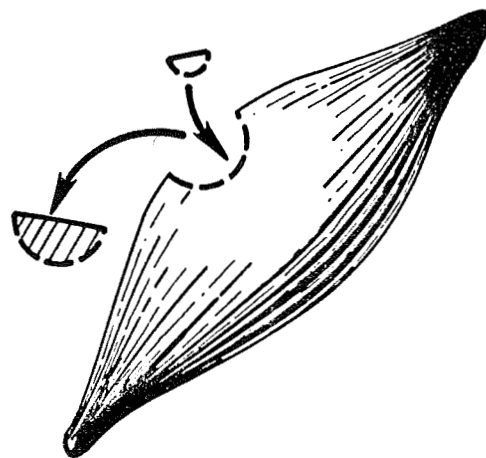
In animal studies, muscle atrophy is most often produced by limb immobilization with casts, denervation, or tenotomy. The atrophic process is monitored by measurement of protein degradation rates and of enzyme activities. In human studies, muscle atrophy in limbs is induced by bedrest and monitored by muscle biopsies, computer-assisted tomography, and analysis of muscle metabolites and enzymes. Noninvasive means of monitoring more sensitively and selectively the mass of individual muscles in human subjects are being developed.

Countermeasures under consideration include different exercise regimes, nutrition, and pharmacological agents. Effective means of preventing and/or treating muscle atrophy are yet to be discovered.

Normal



Weightlessness



Why muscle gets smaller in space. In the normal muscle, formation equals breakdown. In the muscle in weightlessness, formation rate decreases and breakdown increases. As a result, not enough of the muscle in weightlessness is replaced, and this muscle gets smaller in size.

BIOCHEMICAL ADAPTATIONS OF ANTIGRAVITY MUSCLE FIBERS TO DISUSE ATROPHY

F. W. Booth (University of Houston)

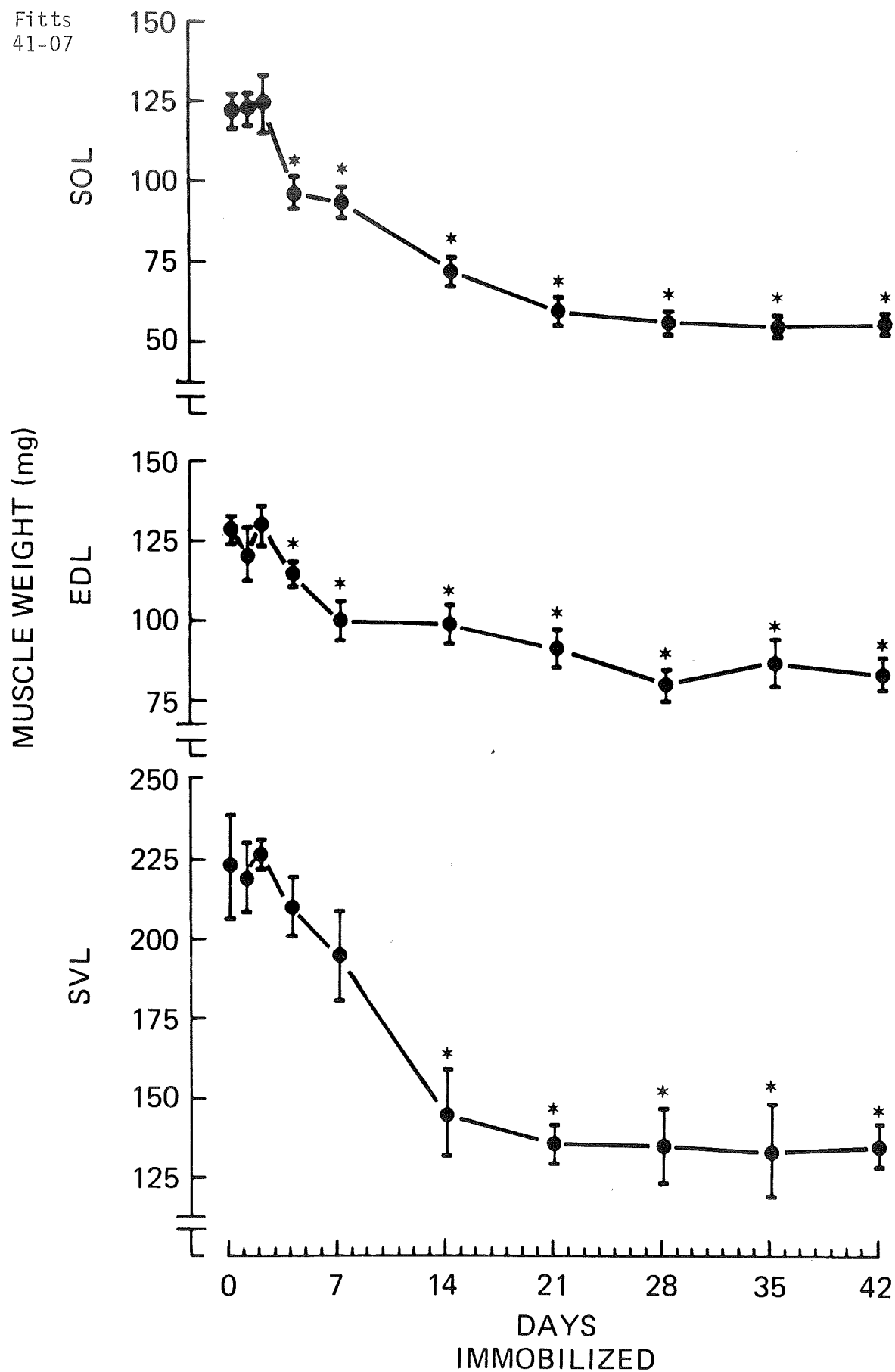
The purpose of these studies is to determine why weightlessness causes skeletal muscles to atrophy. The soleus muscle of rats was selected for examination because it is composed of 85% anti-gravity muscle fibers.

Biochemical and physiological changes occurring during and after 90 days of immobilization were studied. Evidence suggests that the decrease in formation of muscles is a greater cause of atrophy than an increase in muscle breakdown.

Currently being addressed is the question of why muscle formation is slowed by immobilization. It has recently been found that insulin, a growth promoting hormone, does not affect muscles of immobilized limbs as it does normal skeletal muscles. Studies as to how insulin affects muscle formation are being continued. Also being continued are studies to determine the quality and quantity of daily exercise required to prevent muscular atrophy.

PUBLICATIONS

1. Booth, F. W. and Seider, M. J. "Recovery of skeletal muscle after 3 months of hindlimb immobilization in rats." J APPL PHYSIOL 47:435-439, 1979.
2. Seider, M. J., Kapp, R., Chen, C. P., and Booth, F. W. "The effects of cutting or of stretching skeletal muscle in vitro on the rates of protein synthesis and degradation." BIOCHEM J 188:247-254, 1980.



Muscle atrophy with disuse. SOL, slow soleus muscle; EDL, fast extensor digitorum longus muscle; SVL, fast superficial vastus lateralis muscle.

ALTERATIONS IN SKELETAL MUSCLE WITH DISUSE ATROPHY

R. H. Fitts (Marquette University)

This project investigates, via limb immobilization, the physiological and molecular alterations associated with muscle atrophy.

Studies on the rate and extent of change due to disuse in both fast and slow muscles reveal that the slow muscles undergo a greater degree of atrophy and force decrease than the fast muscles, although all muscles exhibit some loss in weight and force. In addition, biochemical studies reveal that slow muscles have an impaired ability to regulate intracellular calcium.

The time course of recovery from six weeks of disuse has been determined. Physiological properties recover within two weeks, with the exception of peak forced output, which requires up to eight weeks. More recent findings suggest that prolonged disuse (90 days or more) requires more time; irreversible changes in muscle function are also possible. Therefore, selected physiological and biochemical properties of muscle are being studied to determine the time course of recovery after 120 days of disuse.

Future plans include a series of experiments to determine if the debilitating effects of weightlessness can be prevented or retarded by a regular program of exercise and to explore the possible role of exercise in postflight recovery.

PUBLICATIONS

None

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PROTEOLYSIS IN MUSCLE ATROPHY

S. Ellis (NASA-ARC)

The focus of this project is a recently discovered lysosomal tripeptidyl aminopeptidase (TAP). Lysosomes have been implicated as a possible contributor to muscle atrophy following denervation, tenotomy, immobilization of limbs, or prolonged spaceflight, but the means by which lysosomal activity is regulated are not understood.

Immunochemical and histochemical methods will be used to localize TAP in the lysosome. In addition, the effect of specific inhibitors of TAP on the proteolytic action of TAP will be assessed. Finally, the amino acid and carbohydrate composition and sequence of pure TAP will be determined.

Since intracellular proteases are the agents by which protein degradation is accomplished, the complete characterization of TAP should contribute to a better understanding of the mechanism of muscle atrophy in immobilization and weightlessness.

PUBLICATIONS

None

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GROWTH FACTORS IN MUSCLE ATROPHY

S. Ellis (NASA-ARC)

According to the neurotrophic hypothesis, a regulatory growth factor which controls the physiological properties of striated muscle as well as its cellular mass can be isolated from the innervating nerves. In this project, an attempt will be made to isolate and characterize this neurotrophic factor in the chicken.

The chemical characterization will consist of determining the distribution of neurotrophic factor among different muscle types and the changes in its concentration in nerve and muscle with activity and work load.

The investigators will also determine in vivo and in vitro effects on acetyl cholinesterase activity, acetyl choline sensitivity, protein synthesis, and muscle mass.

PUBLICATIONS

1. Ellis, S. and Divor, A. R. "Specificity and lysosomal localization of tripeptidyl amino-peptidase." FED PROC 38:832, 1979.

CONCENTRATIONS OF IMMUNOREACTIVE AND BIOASSAYABLE GROWTH HORMONES IN THE PITUITARY GLAND AND PLASMA

	PITUITARY		PLASMA	
	IR-GH $\mu\text{g}/\text{mg}$ TISSUE	BA-GH, $\mu\text{g}/\text{mg}$ TISSUE	IR-GH $\text{m}\mu\text{g}/\text{ml}$	BA-GH, $\text{m}\mu\text{g}/\text{ml}$
HUMAN (NORMAL)	—	—	1.5	300
HUMAN (ACROMEGALIC)	—	—	30	1100
RAT (CONTROL)	30	30	10	500
RAT (48 hr FAST)	15	15	7	1090

EFFECT OF BODY PROTEIN BALANCE ON PLASMA CONCENTRATIONS OF BIOASSAYABLE AND IMMUNOREACTIVE GROWTH HORMONES

TREATMENT	TOTAL BODY NITROGEN, g	IR-GH, $\text{m}\mu\text{g}/\text{ml}$	BA-GH, $\text{m}\mu\text{g}/\text{ml}$
	(MEANS WITH STANDARD ERRORS)		
PRETREATMENT	10.3 ± 0.2	—	—
COMPLETE DIET (10 days)	13.2 ± 0.2	23 ± 9^1	688 ± 20^2
LIMITED PROTEIN DIET (10 days)	10.1 ± 0.2	27 ± 7^1	500 ± 40
CARBOHYDRATE DEFICIENT DIET (10 days)	9.0 ± 0.2	13 ± 4^1	390 ± 30

¹IR-GH VALUES DO NOT DIFFER ($p > 0.05$)

²ALL BA-GH VALUES DIFFER FROM EACH OTHER ($p < 0.05$)

ROLE OF BIOASSAYABLE GROWTH HORMONE IN PROTEIN BALANCE

R. E. Grindeland (NASA-ARC)

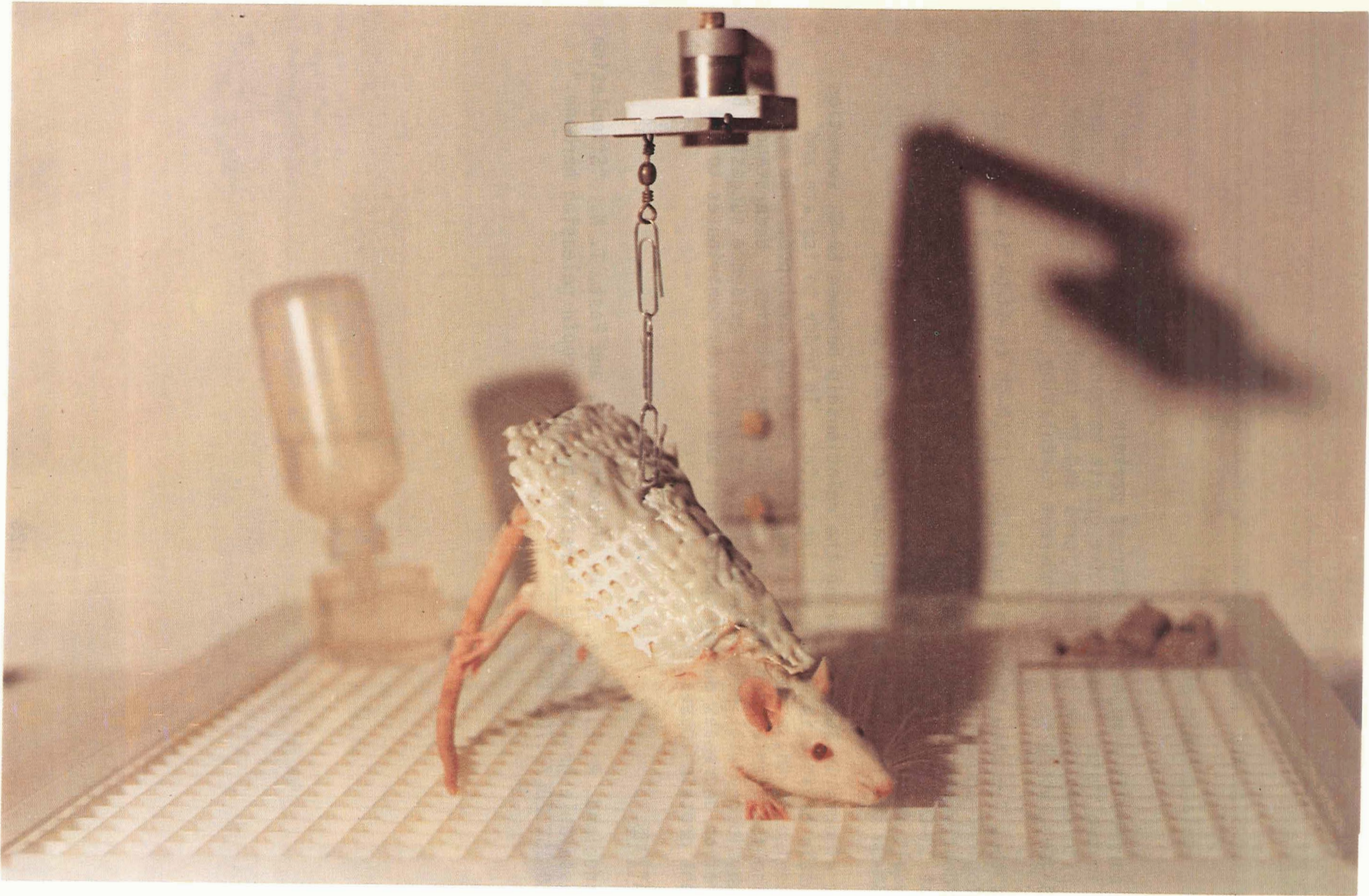
Growth hormone is a major regulator of protein synthesis. The hormone exists in two forms: immunoreactive growth hormone (IR-GH), which occurs in the pituitary gland in storage form, and the newly found bioassayable form (BA-GH), which is the preponderant circulating form.

Results thus far show that the conversion of IR-GH to BA-GH is essential to biological action of the hormones and that the secretion of both is independently controlled. Significantly, plasma concentrations of BA-GH (but not IR-GH) parallel protein balances of animals in metabolic states that result from protein and/or caloric restriction. This suggests that blood BA-GH levels could be an indicator of protein balance.

Current efforts include exploring the relationship between BA-GH secretion and protein balance in muscle wasting states. In order to isolate and characterize BA-GH, a more sensitive assay is being developed. The assay will also facilitate more extensive physiological studies. Understanding BA-GH physiology will help determine if, as indirect evidence suggests, BA-GH secretion decreases during spaceflight and thereby contributes to the in-flight protein losses.

PUBLICATIONS

1. Grindeland, R. E., Yang, S. H., Osborne, S., and Fast, T. N. "Stimulation of bioassayable growth hormone secretion by thyrotropin releasing hormone." *PHYSIOLOGIST* 22(3):70, 1979.



Rat in space model. The rat is suspended by a back harness, with front paws touching the grating, hind limbs mid-air, and with head tilted downward at 30° .

PROTEIN TURNOVER OF ATROPHIED AND HYPERTROPHIED ANTIGRAVITY MUSCLES
FROM THE RAT

H. S. Ginoza (NASA-ARC)

A model which simulates many biochemical and physiological changes found in rats returned from spaceflight is used to study protein metabolism in antigravity muscles. In this model, a rat is suspended from a back harness with front paws touching the floor and hind limbs hanging mid-air. The head is tilted downward at a 30° angle to mimic the fluid shift observed in space. The role of insulin and glucocorticoids in muscle atrophy is being studied.

The soleus muscles of suspended rats lose 40-50% of muscle mass during a week of confinement. The loss is due to a reduction in protein synthesis. This differs from the atrophy of denervated muscles in which the loss is due to an increased rate in protein breakdown. Antigravity muscles in rats exposed to 4.1G force for 1-12 weeks exhibited distinct hypertrophy. The increased size can be attributed to a high rate of muscle protein synthesis, the reverse of atrophic mechanism.

Included in the present effort will be the determination of whether calcium ions from bone resorption are associated with the induction of muscle protein degradation.

PUBLICATIONS

1. Fuller, D. D., Ginoza, H. S., Morey, R. E., and Oyama, J. "Proteolytic activity of atrophied and hypertrophied soleus muscle from rats." FED PROC 39:818, 1980.

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5. BLOOD ALTERATIONS

UPN	PI	SHORT TITLE
199-20-51-01	Taylor	Morphometric Blood Cell Analysis
199-20-51-03	Alfrey	Blood Volume Regulation
199-20-51-05	Dunn	Erythropoietin Inhibition
199-20-51-09	George	Platelet Function
199-20-52-01	Leon	Post-Hypoxia Red Blood Cell Response
199-20-52-03	Landaw	Membrane Proteins and Erythrocyte Survival
199-20-54-01	Castleman	Image Analysis Hematology

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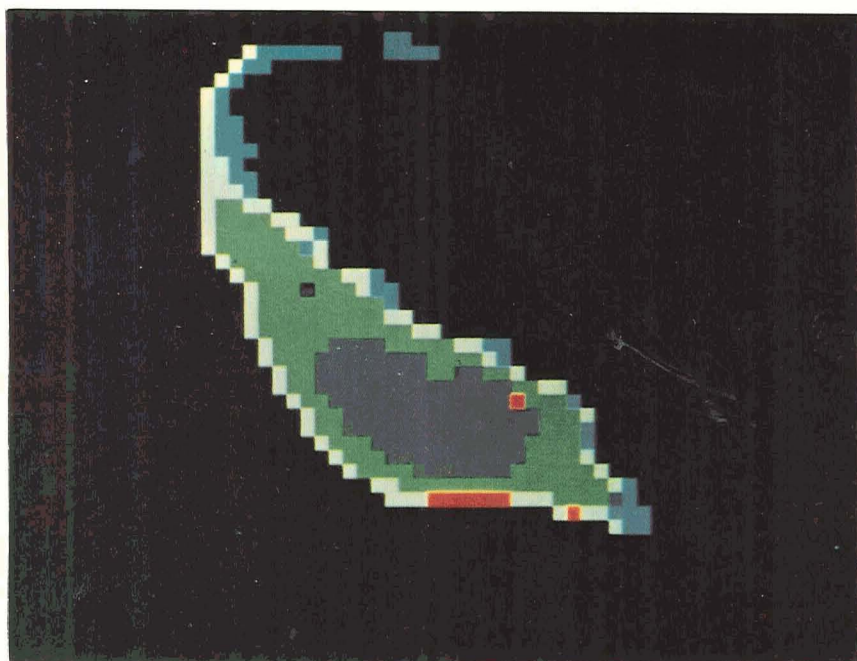
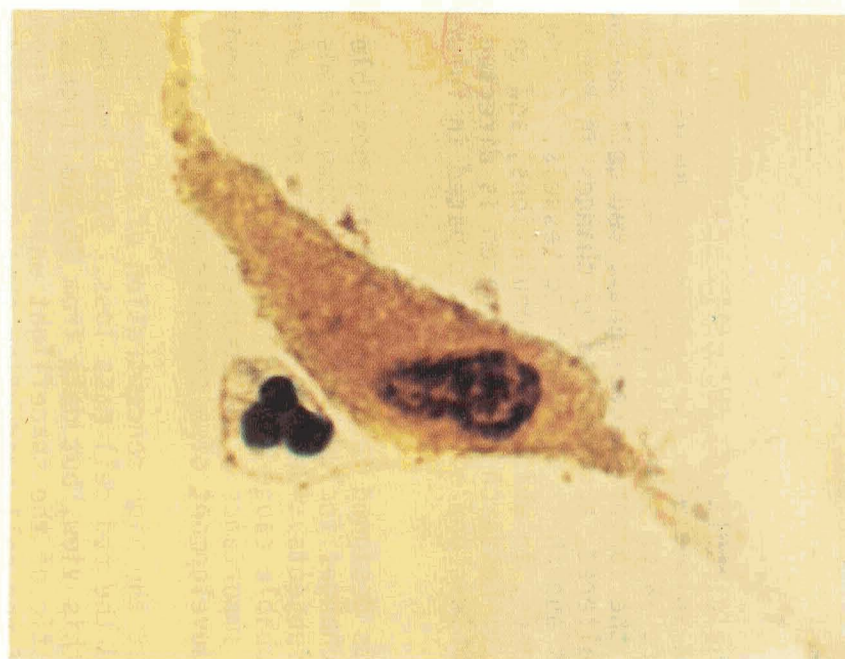
INTRODUCTION

A significant reduction in the circulating red cell mass and a rapid, sustained depletion in plasma volume were first observed during the Gemini missions. These findings were later substantiated during subsequent Apollo and Skylab missions. During the longer spaceflights, red cell surface topography and structure were altered, accompanied by changes in the structure of other types of blood cells and their transporting vessels. Changes were also noted in red cell membranes, in white cell populations, and in some plasma protein concentrations. Research in the program is directed toward an understanding of these problems and of those anticipated in future missions.

Ground-based research projects designed to investigate the possible mechanisms of the observed blood changes include spaceflight simulations and involve both human and animal subjects. Because most of the data suggest a reduced production as the probable cause of the red cell mass loss, erythropoiesis studies are of great importance. The complexity of the erythropoietic process is addressed in the development of a computer model.

It was initially proposed that the high concentration of oxygen in the spacecraft atmosphere induced the red cell mass loss. Data from Gemini and Apollo flights corroborated this view, but data from Skylab flights did not. Some other factor characteristic of the spaceflight environment appears to be causing the suppression of red cell production that is not immediately relieved with a return to Earth, although in longer flights such as the Skylab 4 mission, the red cell mass seems to begin recovery before re-entry.

Supplementary efforts in this program involve the definition and testing of procedures and equipment for ground-based and in-flight investigations. Analytical procedures under development include the *in vitro* assessment of blood cell functional capacity using structural and biochemical techniques, in-flight microprocedures for blood sampling, processing, and analysis, and automated data analysis and cell classification techniques. Other areas of research to which these procedures apply include: changes in blood coagulation during spaceflight; changes in serum enzymes, metabolites and lipids; and studies of the rheological properties of blood.



Digital image analysis of malignant bronchial epithelial cell. Left: Photomicrograph of the malignant cell. Right: Digitized version of same cell, collected at three different wavelengths (430 nm, 530 nm, and 590 nm). At this time, computer classification and cytopathologists' classifications are approaching 90% agreement.

MORPHOMETRIC ANALYSIS OF CELLS OF THE BLOOD

G. R. Taylor (NASA-JSC)

One of the principal objectives of this effort is to develop the analytical capabilities to study minute cellular changes resulting from diseases and drug-induced changes in cell immunological responses. Computer algorithms have been developed to analyze the nuclear architecture of cells, facilitating a differentiation of normal and abnormal cells. Also, new procedures allow the use of smaller quantities of blood for morphometric analysis.

Recently, it has become possible to differentiate between the major lymphocyte subclasses, the thymus-dependent (T) and thymus independent (B), on the basis of computed digital image analysis. This procedure uses a dye, which differentially stains DNA and RNA, and highly specialized equipment, including a microscope, video camera, and computer.

The visual image of the lymphocyte is converted into a digital matrix which provides data in numerical form for rapid computer processing and storage. Thus, both qualitative and quantitative features of lymphocytes can be assessed. The value of the digitized matrix is particularly high when the cells are visually indistinguishable.

PUBLICATIONS

None

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INFLUENCE OF SPACEFLIGHT ON REGULATION OF BLOOD VOLUME

C. Alfrey (Baylor College of Medicine)

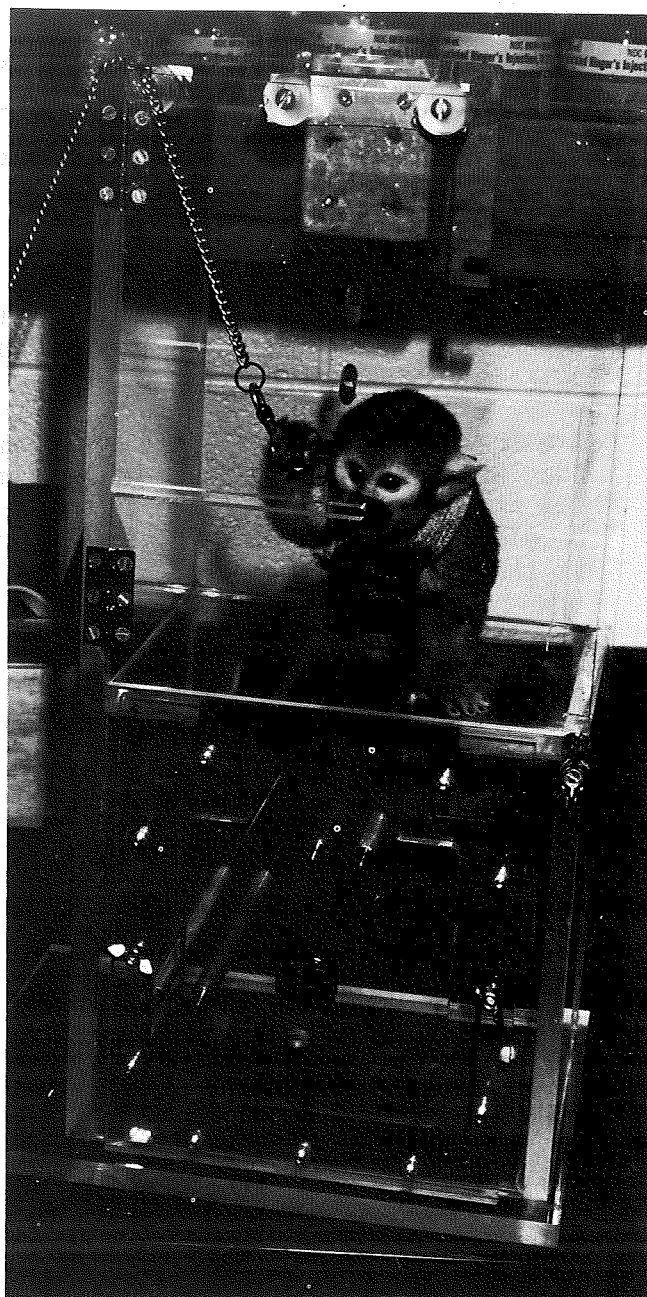
The objective of this project is to establish the rat as a model in which to simulate changes in plasma volume (PV) and red cell mass (RCM).

While the literature contains many descriptions of research studies requiring a single measurement of RCM in the rat, multiple RCM determinations for the same animal is not reported. Part of the problem is that the withdrawal of large volumes of blood required for multiple RCM determinations affects the validity of the data.

A method which requires only micro amounts of blood has been developed such that RCM and PV can be determined simultaneously at four-week intervals. The new method can detect changes of five percent or more. The methodology developed for iron kinetic studies (red cell production rate) can be repeated at the same frequency.

PUBLICATIONS

None



Squirrel monkey in Lower Body Positive Pressure (LBPP) machine.

INFLUENCE OF SPACEFLIGHT ON ERYTHROPOIETIN CONCENTRATION AND INHIBITION

C. D. R. Dunn (NASA-JSC)

Much effort has been directed toward identifying the cause of anemia in dehydrated mice, which show characteristics similar to those of man in space: reduced plasma volume, resulting in an increased concentration of blood cells (hemoconcentration), and negative energy balance. Animal studies, supported by computer simulations, suggest that the primary cause is negative energy balance and that hemoconcentration plays only a minor role in causing the anemia. Dehydration did not seem to increase the destruction of red blood cells. These studies indicate the importance of maintaining normal fluid and energy balance to the proper functioning of the erythropoietic process.

Recently, research has begun on red blood cell production in squirrel monkeys exposed to lower body positive pressure, a procedure that induces a headward shift of body fluids. This animal system should provide further information on the etiology of anemia in spaceflight.

PUBLICATIONS

1. Dunn, C. D. R. and Lange, R. D. "Erythropoietic effects of space flight: Further studies in a potential animal model." ACTA ASTRONAUTICA 6:725-732, 1979.
2. Dunn, C. D. R. "The effect of food or water restriction on erythropoiesis in mice. Relevance to the 'anemia' of space flight." AM J PHYSIOL 238:R301-R305, 1980.
3. Dunn, C. D. R. and Lange, R. D. "Erythropoietin: Assay and characterization." In: Topical Reviews in Haematology, S. Roath, ed. John Wright & Sons Ltd., Bristol, Volume I, 1980, pp. 1-32.

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199-20-51-09

SEP 1980

THE EFFECT OF STRESS ON HUMAN BLOOD PLATELETS

J. N. George (University of Texas)

The studies in this recently initiated project will define the extent of platelet activation during stress and will help to understand the reasons for the increased risk of thromboembolic disorders during immobilization.

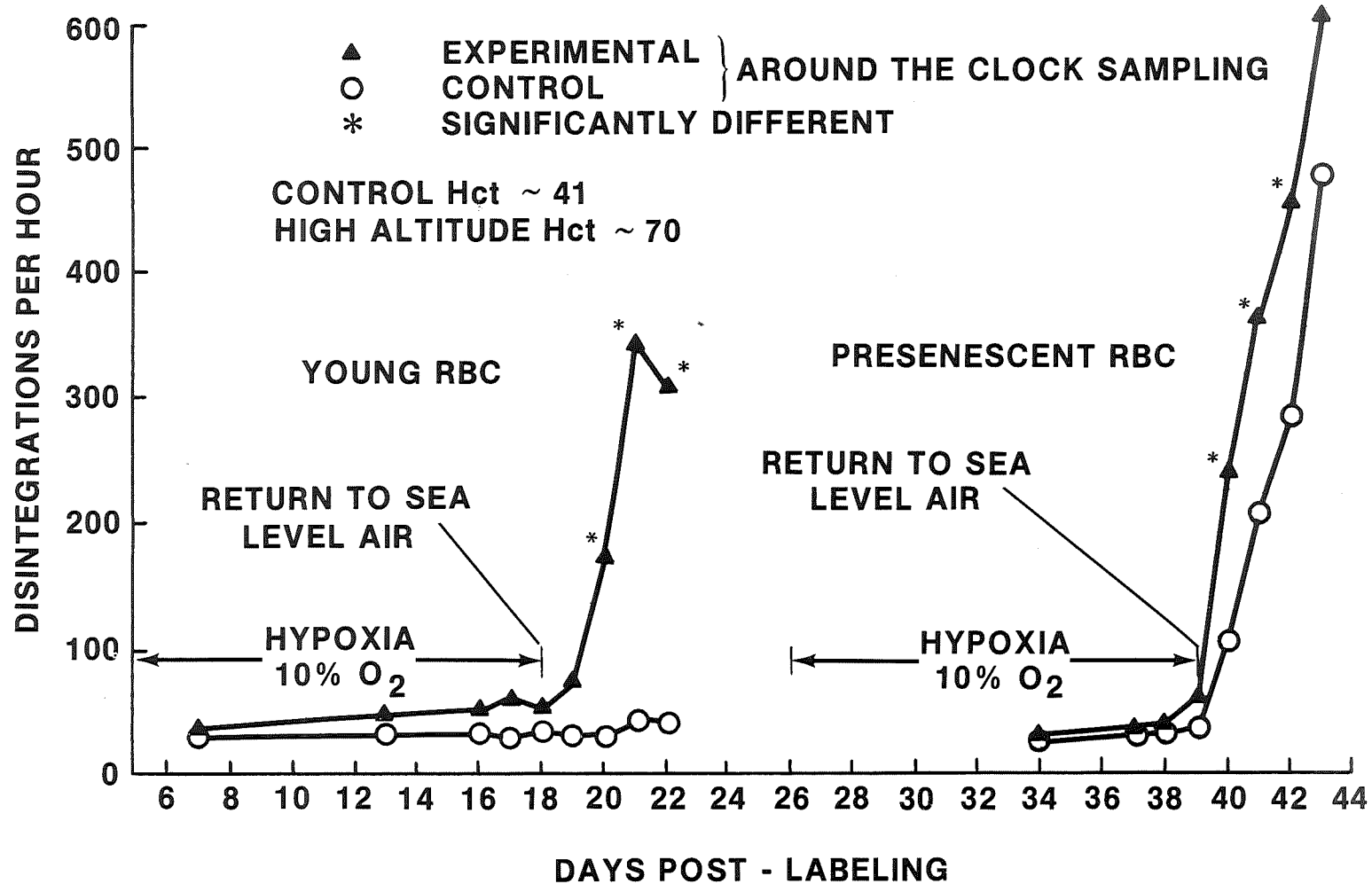
Activation of platelets during circulation in vivo will be measured by secretion of the platelet-specific granule protein, termed platelet factor 4 (PF4), which is measured by radioimmunoassay of cell-free plasma. Circulating platelet aggregates will be measured as an additional manifestation of platelet activation. These studies will be performed with normal subjects during maximal physical exercise, standardized on a bicycle ergometer or treadmill.

If abnormal platelet activation, which may be associated with an increased risk of thrombosis, is detected during these studies, drugs which may prevent these changes will be studied.

PUBLICATIONS

None

EFFECT OF NORMOXIA ON RBC DESTRUCTION IN THE RAT FOLLOWING HYPOXIA-INDUCED POLYCYTHEMIA AS MEASURED BY ^{14}CO OUTPUT



CONTROLLERS OF RED BLOOD CELL MASS DURING HYPOKINESIS

H. A. Leon (NASA-ARC)

When rats are exposed to reduced oxygen or hypoxia, more red blood cells (RBC) are produced. When these rats are returned to normal air, a remarkable increase in hemolysis occurs which lasts about six days. The rats apparently have a sensor to detect a relative excess of RBC, coupled to a mechanism that destroys them.

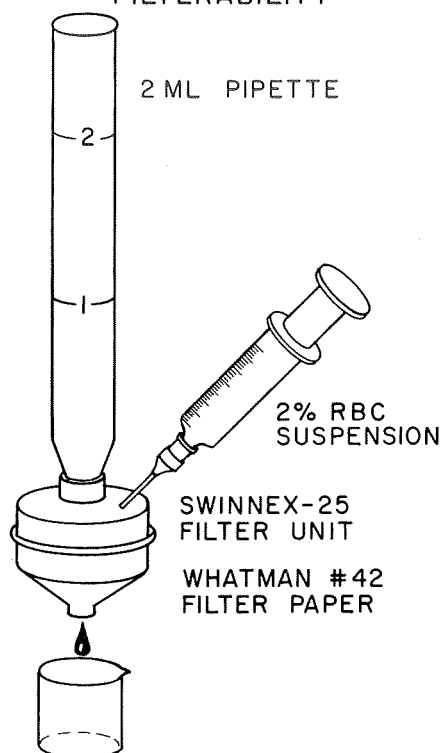
Considerable progress has been made in elucidating the mechanism of hemolysis. A factor which causes hemolysis has been identified in the blood platelets.

Further experimentation will demonstrate directly whether platelets are involved and determine how they facilitate hemolysis. Also to be investigated is how changes in blood oxygen content trigger the release of the platelets, since blockage of this initial step may prevent subsequent hemolysis.

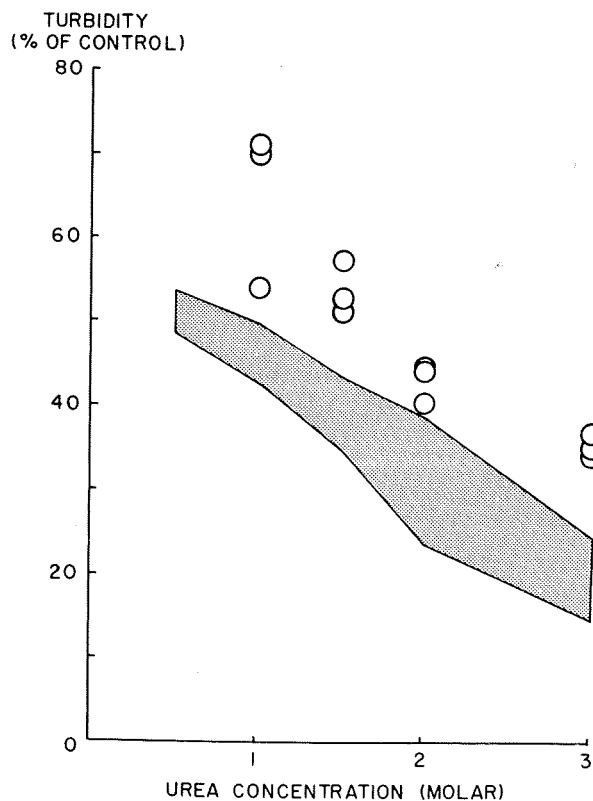
PUBLICATIONS

1. Leon, H. A., Willis, A., Landaw, S. A., Fisher, J., and Fleming, J. "Effect of prostaglandin E_2 (PGE_2) on guinea pig and human red cells." FED PROC 39(3):391, 1980.
2. Leon, H. A. and Fleming, J. "Extremes of urine osmolality: Lack of effect on red blood cell survival." AM J PHYSIOL 139 (Cell Physiol 8): C27-31, 1980.
3. Leon, H. A., Serova, L. V., and Landaw, S. A. "Effect of weightlessness and centrifugation on red-cell survival in rats subjected to spaceflight." AVIAT SPACE ENVIRON MED 51(10):1091-94, 1980.

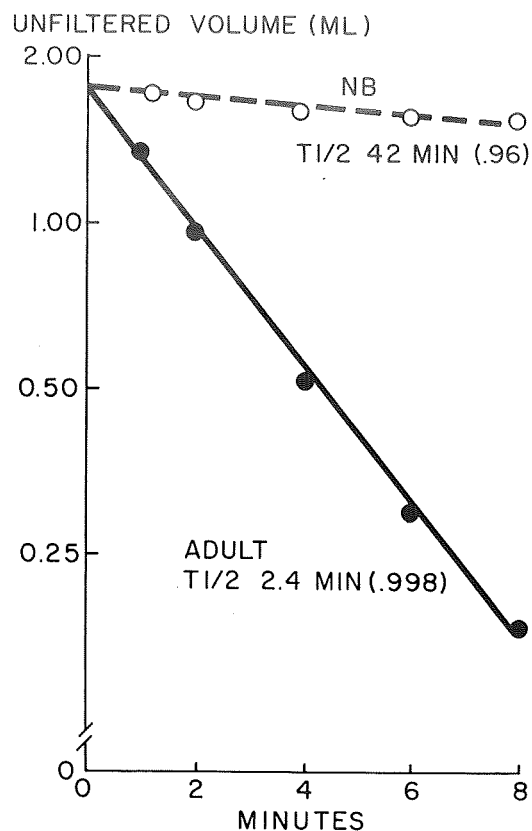
PROCEDURE FOR TESTING RBC FILTERABILITY



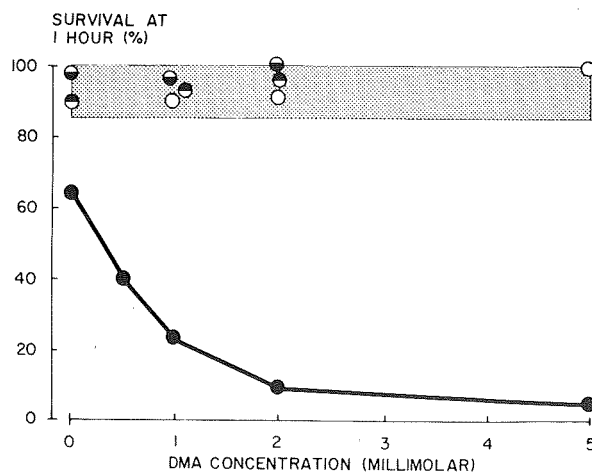
Method. A 2% suspension of RBC in buffer is transferred to pipette with attached syringe. Unfiltered volume is noted every 0.5 minutes.



Triton-treated RBC ghosts. The cytoskeleton of newborn rat RBC is less dissociable in urea than that of adult rat RBC. Shaded region is the range for normal adult rats. Open circles (o) indicate normal newborn rats.



Results. Adult rat RBC (●-●) are much more filterable (deformable) than newborn rat RBC (o---o). Correlation coefficients for the least-squares best fit are in parentheses. T_{1/2} = Filtration half-time.



Rat RBC survival with and without dimethyladipimide (DMA). The survival in circulation of newborn rat RBC (●-●) is reduced, compared to adult rat RBC (o). Treatment with DMA, an agent which cross-links RBC membrane proteins selectively, worsens survival of newborn RBC.

MEMBRANE PROTEINS AND ERYTHROCYTE SURVIVAL

S. A. Landaw (Syracuse Veterans Administration)

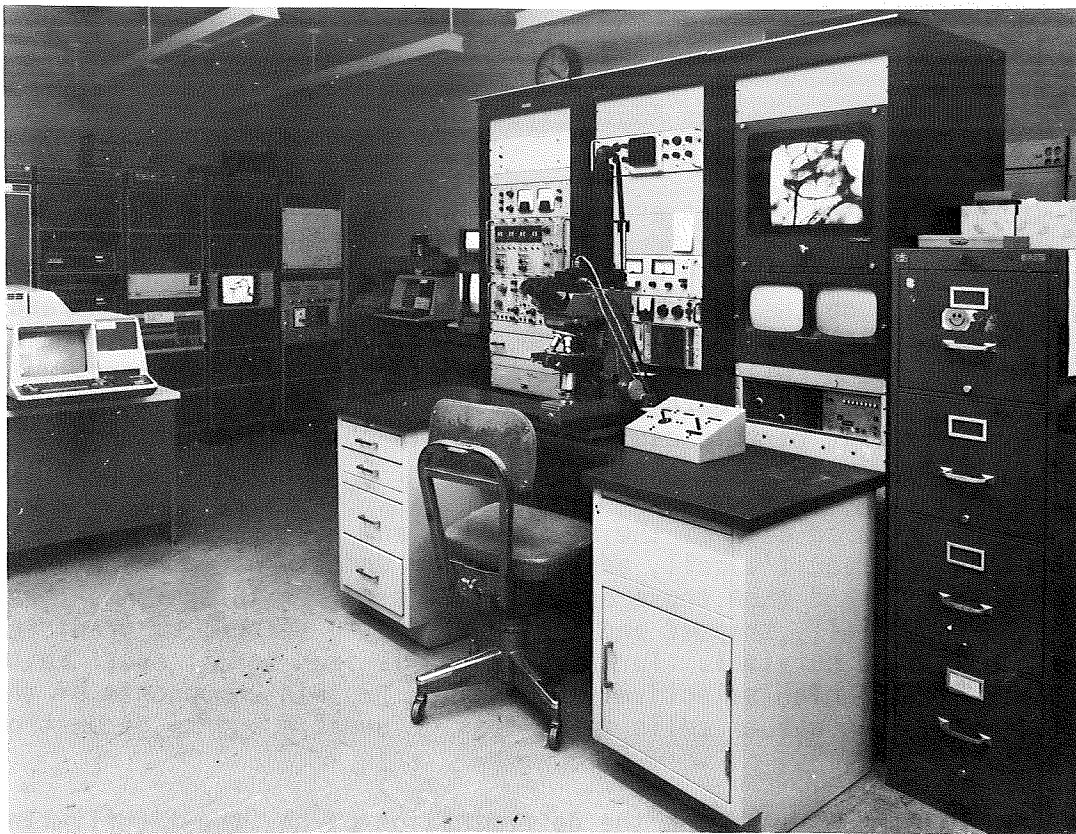
Initial studies have shown that external influences, such as might be present in prolonged space missions (oxidants, drugs, alterations in acid-base balance) have profound effects on the red blood cell membrane. Most of these influences cause the underlying "skeleton" of the red cell membrane to "stiffen," resulting in a cell with decreased ability to deform within the circulation. Such cells are trapped and destroyed in the spleen, an organ uniquely qualified to detect such alterations. This membrane change may play a significant part in causing the anemia observed in returned astronauts.

It appears that the red cell of the newborn rat and newborn man are less deformable than the adult's cell, and that their underlying membrane skeletons are more tightly linked than those of the adult's cell. In the rat, these cells are preferentially trapped and destroyed in the spleen, as predicted, leading to shortened survival. Further, red cells from normal adult rats treated with agents which selectively cross-link protein components of the membrane skeleton cause such cells to be less deformable and to be destroyed in the spleen.

Future plans will revolve around the determination of how the tightly-linked structure is achieved, how it can be modified by external influences, and of strategies to predict whether individuals might be expected to develop alterations in RBC survival on exposure to certain adverse external influences.

PUBLICATIONS

1. Landaw, S. A., Rathbun, S. C., and Guancial, R. L. "Evidence for a tightly linked spectrin lattice in newborn red blood cells." PEDIATR RES 14:536, 1980.
2. Landaw, S. A., Rathbun, S. C., and Guancial, R. L. "The effect of spectrin cross-linking on red blood cell membrane properties and survival." PEDIATR RES 14:536, 1980.



Automated Light Microscope System at JPL. The hardware consists of a Zeiss photomicroscope with computer controlled stepping stage. The vidicon TV camera of the Spatial Data Systems image digitizer is mounted on the microscope, and the entire system is controlled by a PDP-11 computer. The system executes the mini-VICAR image processing software system and a variety of additional programs developed for bone and cell image analysis.

BONE AND CELL IMAGE ANALYSIS

K. R. Castleman (JPL-CIT)

This project supports the joint parallel development of microscope image analysis techniques in three different centers: Jet Propulsion Laboratory, NASA-Ames Research Center, and NASA-Johnson Space Center. Computer-controlled light microscope systems and digital image analysis programs have been developed in each center.

The purpose of this project is not so much to develop the systems, as it is to coordinate the three projects. Thus it prevents duplication of effort, facilitates a sharing of software and system development and experience, and fosters standardization of hardware, software, and data formats to benefit all three laboratories.

These systems can locate and measure objects and structures in a variety of microscope specimens. Examples include muscle fibers in histochemically prepared biopsy sections, squamous cells from the lungs and the uterine cervix, tetracycline-labelled bone cross sections, red and white blood cells, and human chromosomes.

Also possible is the measurement of a variety of size, shape, optical density, and texture parameters to quantify spaceflight induced physiological changes. This quantitative information is essential to studies of the effects of long-term spaceflight on humans.

PUBLICATIONS

None

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6. FLUID AND ELECTROLYTE CHANGES

UPN	PI	SHORT TITLE
199-20-61-01	Leach	Biochemical Control of Fluid Electrolyte
199-20-61-02	Epstein	Sodium Homeostasis and Renin-Aldosterone
199-20-61-06	Moore-Ede	Fluid and Electrolyte in Primates
199-20-61-07	Hollenberg	Angiotensin Antagonists
199-20-62-02	Severs	CNS Control of Salt/Water Balance
199-20-62-03	Luetscher	Gravitational Stress in Fluid Balance
199-20-62-04	Holton	Renal Receptor Sensitivity
199-20-62-05	Gann	Hormonal Control of Blood Volume

INTRODUCTION

During the first 24-48 hours of Skylabs 3 and 4, five out of six crewmen showed negative balances in sodium chloride and water. After 3-4 days in flight, a steady state in sodium and water seemed to have been reached. The more gradual weight loss that continues throughout spaceflight may be attributable to loss in tissue mass. The first three days of postflight recovery is characterized by a positive balance of salt and water, much like a mirror image of the negative balance seen in early flight.

Rapid redistribution of body fluids from the legs toward the head and resultant central volume expansion may cause the increased urinary excretion of sodium and water, in addition to that of potassium and calcium. However, the exact mechanism is unclear and could involve plasma protein concentration, aldosterone, anti-diuretic hormone, putative natriuretic* hormones, and changes in renal hemodynamics. Unfortunately, information concerning these particular changes are not available for the first few hours of flight, the period during which the rapid fluid shift occurs.

This RTOP seeks to investigate in ground-based studies changes in fluid and electrolyte metabolism and in renal function previously identified during manned spaceflight programs, to develop appropriate countermeasures and to design and test advanced instrumentation as necessary.

* That which inhibits the reabsorption of cations (particularly sodium) from urine, thus contributing to increased excretion of the cation.

RENAL AND ENDOCRINE STUDIES DURING EARLY PHASE OF ANTIORTHOSTATIC
HYPOKINESIA

C. S. Leach (NASA-JSC)

The primary objective of this new research is to determine the responses of the kidney to weightlessness and to investigate the mechanisms by which these responses are elicited. To do this, a simulation technique is required that qualitatively and temporally induces changes similar to those of spaceflight.

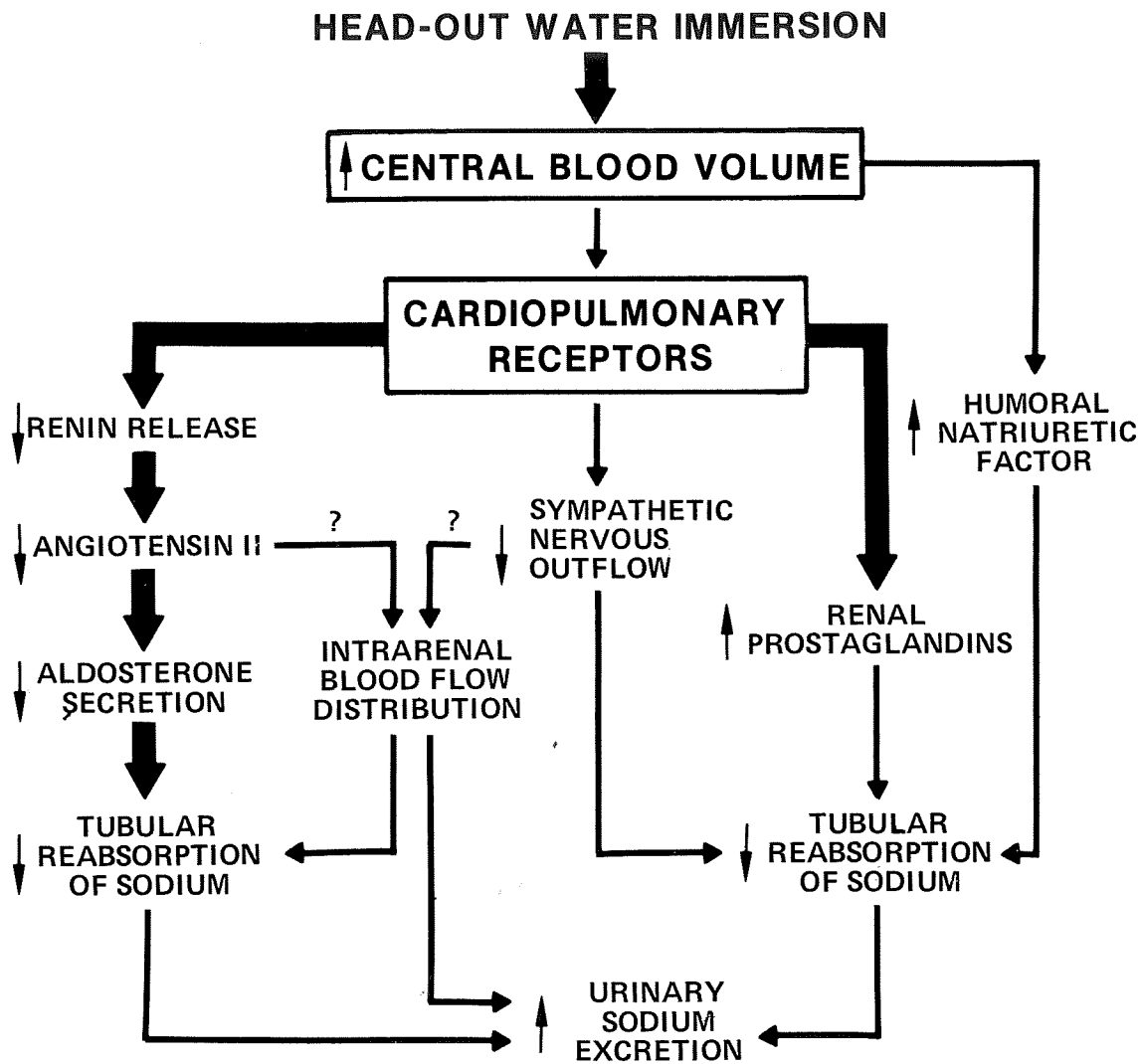
The renal responses to antiorthostatic bedrest will be evaluated and compared with renal responses to horizontal bedrest. Measurements include:

- a) Indices of renal function including excretion rates, clearances, glomerular filtration rate, and renal blood flow;
- b) Body fluid volumes including plasma, extracellular fluids, and total body water; and
- c) Electrolyte, protein, and hormone levels in plasma and urine.

In conjunction with other measurements of fluid-electrolyte status, the results of the renal function tests proposed will provide (1) a basis for an integrated understanding of renal function during two types of hypokinesia and (2) a point of departure for designing future experiments to study the mechanisms involved in the adaptation to weightlessness.

PUBLICATIONS

None



Effect of immersion on natriuresis. Mechanisms whereby immersion-induced central hypervolemia induces natriuresis are schematized. Heavy arrows indicate pathways for which evidence is available. (Adapted from Epstein, *PHYSIOL REV* 58:550, 1978.)

SODIUM HOMEOSTASIS AND RENIN-ALDOSTERONE RESPONSIVENESS DURING SIMULATED WEIGHTLESSNESS

M. Epstein (VA Medical Center, Miami)

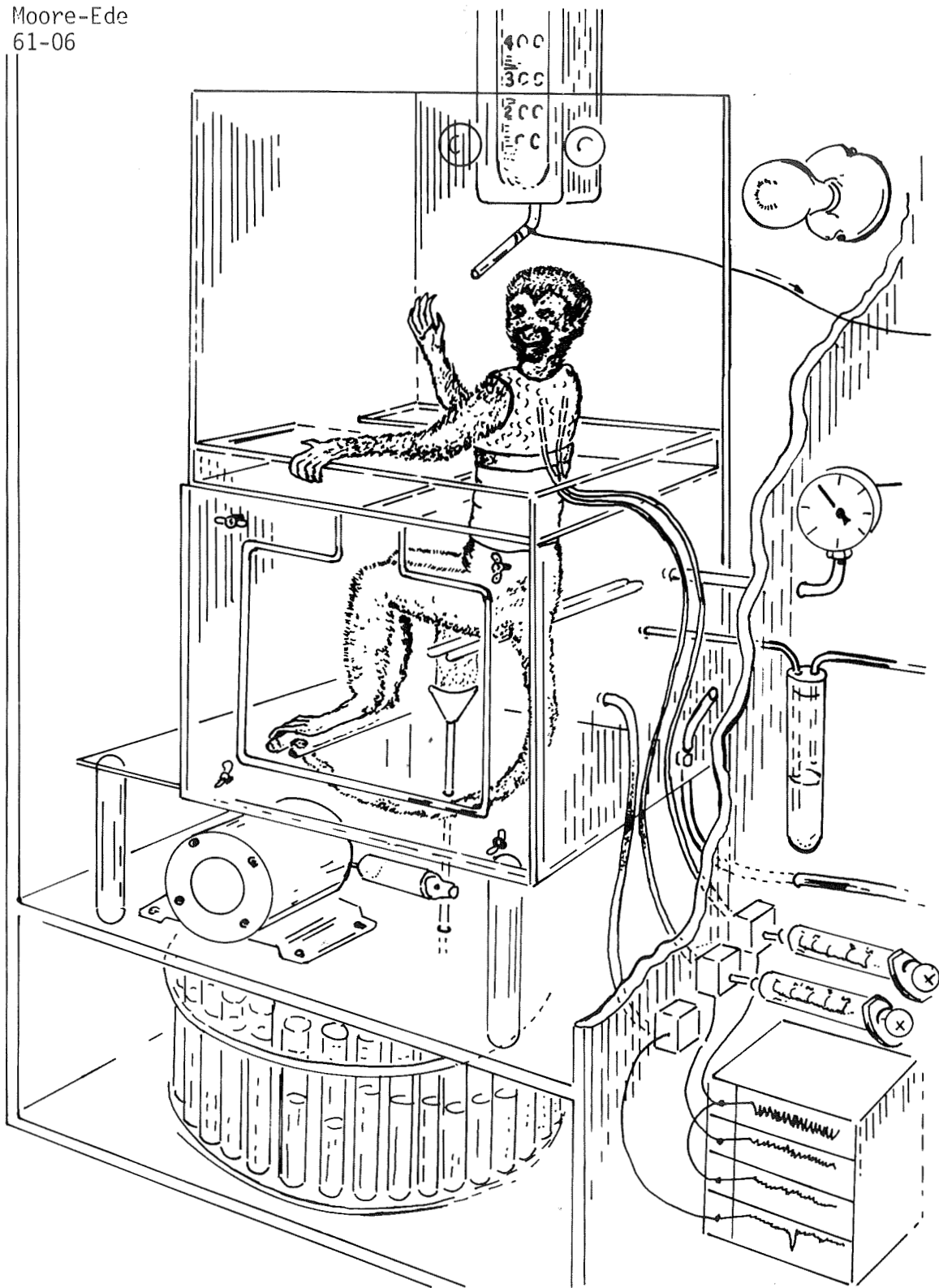
Water immersion has been used as a ground-based analog for weightlessness in a study of volume homeostasis and salt and water excretion. Determination of the magnitude and temporal profile of renin-aldosterone suppression during immersion has lent support to the postulate that the renin-aldosterone changes observed during manned spaceflight are attributable to a redistribution of the circulating blood volume and that they contribute to the observed salt excretion. The exact mechanism of this action is yet unclear. That renal prostaglandin E excretion is also augmented during immersion suggests the involvement of this hormone system in water and salt regulation.

A related subject matter of great controversy is whether or not the salt and water loss results in a new steady-state. Throughout a prolonged period of water immersion, salt and water losses seem to continue unabated. It appears that as long as the thoracic region senses high fluid volume, that adaptation remains incomplete.

The following factors are under continued investigation: the renin-aldosterone system, kallikrein-kinin, renal prostaglandin, vasopressin, and their effects in modulating sodium and water homeostasis.

PUBLICATIONS

1. Epstein, M., Re, R., Preston, S., and Haber, E. "Comparison of the suppressive effects of water immersion and saline administration on renin-aldosterone in normal man." J CLIN ENDOCRINOL METAB 49:358-363, 1979.
2. Epstein, M., Lifschitz, M. D., Re, R., and Haber, E. "Dissociation of renin-aldosterone and renal prostaglandin E during volume expansion induced by immersion in normal man." CLIN SCI 59:55-62, 1980.
3. Epstein, M., DeNunzio, A. G., and Ramachandran, M. "Characterization of the renal response to prolonged immersion in normal man. Implications for an understanding of the circulatory adaptation to manned spaceflight." J APPL PHYSIOL 49:184-188, 1980.



Fluid and electrolyte studies in primate model system. Squirrel monkey is in lower body positive air pressure (LBPP) instrument.

FLUID AND ELECTROLYTE STUDIES IN PRIMATE MODEL SYSTEM

M. C. Moore-Ede (Harvard Medical School)

In squirrel monkeys subjected to a lower body positive pressure (LBPP) chair, fluids shift into the upper body as during weightlessness, and there is an increase in central venous pressure, accompanied by a prompt reflex increase in urine flow and sodium excretion (Henry-Gauer reflex). Circadian adaptive mechanisms seem to prevent nocturnal urine and sodium excretion. At night, response to LBPP is suppressed and the renal reflex is not activated.

Potassium loss and the mechanisms behind it are being studied in detail also. During previous space missions (especially Apollo), plasma levels of potassium were extremely low, resulting possibly in cardiac arrhythmias. The greatest urinary loss of potassium occurs during the first 12 hours of LBPP. Long-term LBPP leads to a fall in plasma potassium. The squirrel monkey model is being further developed to examine mechanisms of potassium loss during spaceflight.

PUBLICATIONS

1. Moore-Ede, M. C., Kass, D. A., Sulzman, F. M., and Fuller, C. A. "Chronic central vascular expansion induces hypokalemia in conscious primates." PROC INT UNION PHYSIOL SCI 14:594, Budapest, Hungary, 1980.
2. Kass, D. A., Sulzman, F. M., Fuller, C. A., and Moore-Ede, M. C. "Natriuresis and diuresis induced by cephalad fluid shifts in a conscious primate: Nocturnal suppression of the response." PHYSIOLOGIST 22(4): 66, 1979.

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ANGIOTENSIN ANTAGONISTS AND VOLUME HOMEOSTASIS

N. K. Hollenberg (Harvard Medical School)

The renin-angiotensin-aldosterone system is a possible mechanism by which the body may rid itself of salt and water under weightless conditions. The delineation of its role in fluid volume control has been made possible by the recent development of agents that block this system.

When a deficit in water and salt occurs (e.g., in astronauts upon return to Earth), angiotensin responds in several ways to make up the loss: (1) it constricts blood vessels to help maintain blood pressure; (2) it constricts renal blood vessels to help retain sodium and water; and (3) it stimulates adrenal aldosterone release in order to promote sodium retention by the kidneys. It appears that angiotensin receptors in the different systems (e.g., adrenal gland, peripheral blood vessels and renal blood vessels and glomerulus) differ enough that very specific blocking agents can be developed which will help elucidate the action of angiotensin.

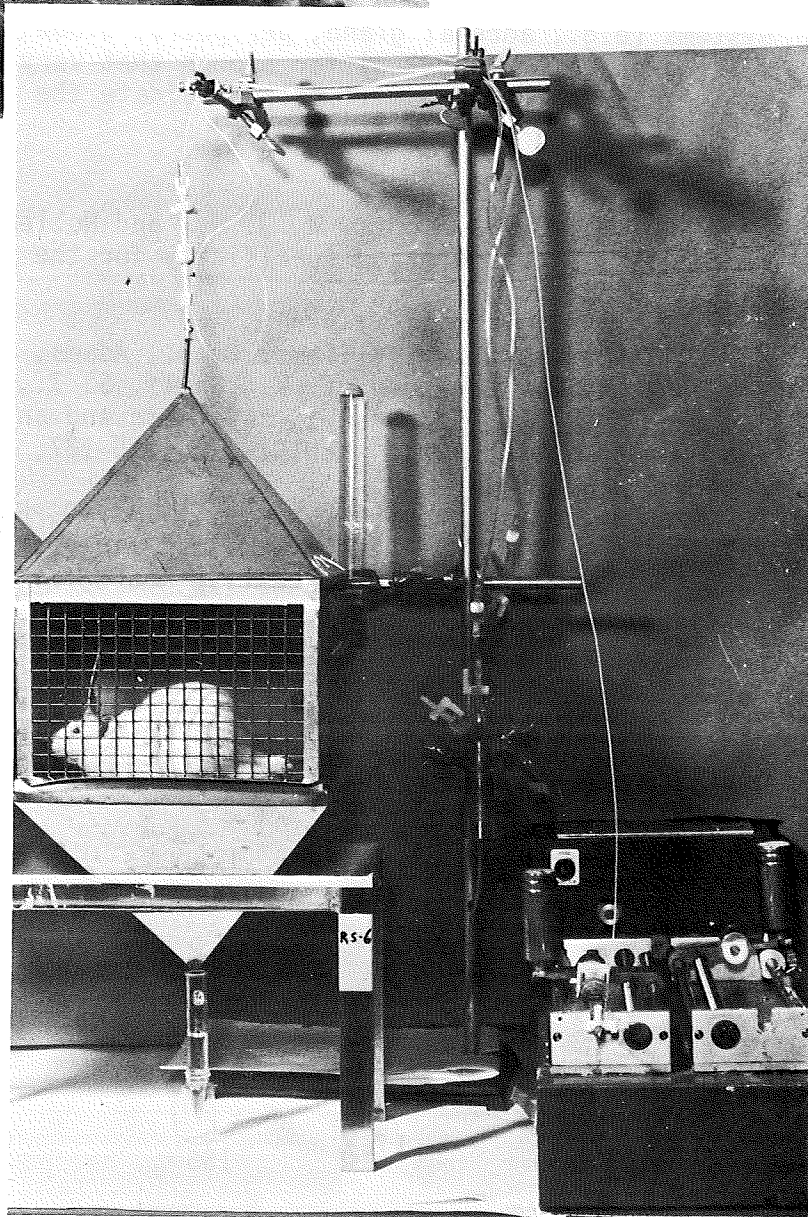
PUBLICATIONS

1. Taub, K. J., Caldicott, W. J. H., and Hollenberg, N. K. "Angiotensin antagonists with increased specificity for the renal vasculature." J CLIN INVEST 59:528-535, 1977.
2. Hollenberg, N. K., Williams, G. H., Adams, D. V., Moore, T. J., Brown, C., Borucki, L. J., Leung, F. K., Bavli, S. Z., Solomone, H. S., Passan, D., and Dluhy, R. J. "Response to saralasin and angiotensin's role in essential and renal hypertension." MEDICINE 58:115-127, 1979.
3. Dzau, V. J., Colucci, W. S., Williams, G. H., Curfman, G., Meggs, L., and Hollenberg, N. K. "Sustained effectiveness of converting enzyme inhibitor in patients moribund with congestive heart failure." NEW ENGL J MED 302: 1373-1379, 1980.



Conscious rat wears a headset containing catheters in a carotid artery and a lateral brain ventricle. Catheters exit through a spring for remote access.

Rat, prepared as above, is shown in cage assembly. The rat is undergoing infusion into the lateral brain ventricle, while its water intake and urine output are being monitored.



CNS MECHANISMS REGULATING SALT/WATER BALANCE

W. B. Severs and L. C. Keil (Pennsylvania State University)

Blood and urine samples of astronauts have revealed changes in angiotensin and vasopressin. Understanding the mechanisms of action of these hormones will help in understanding the fluid and electrolyte changes that occur during spaceflight.

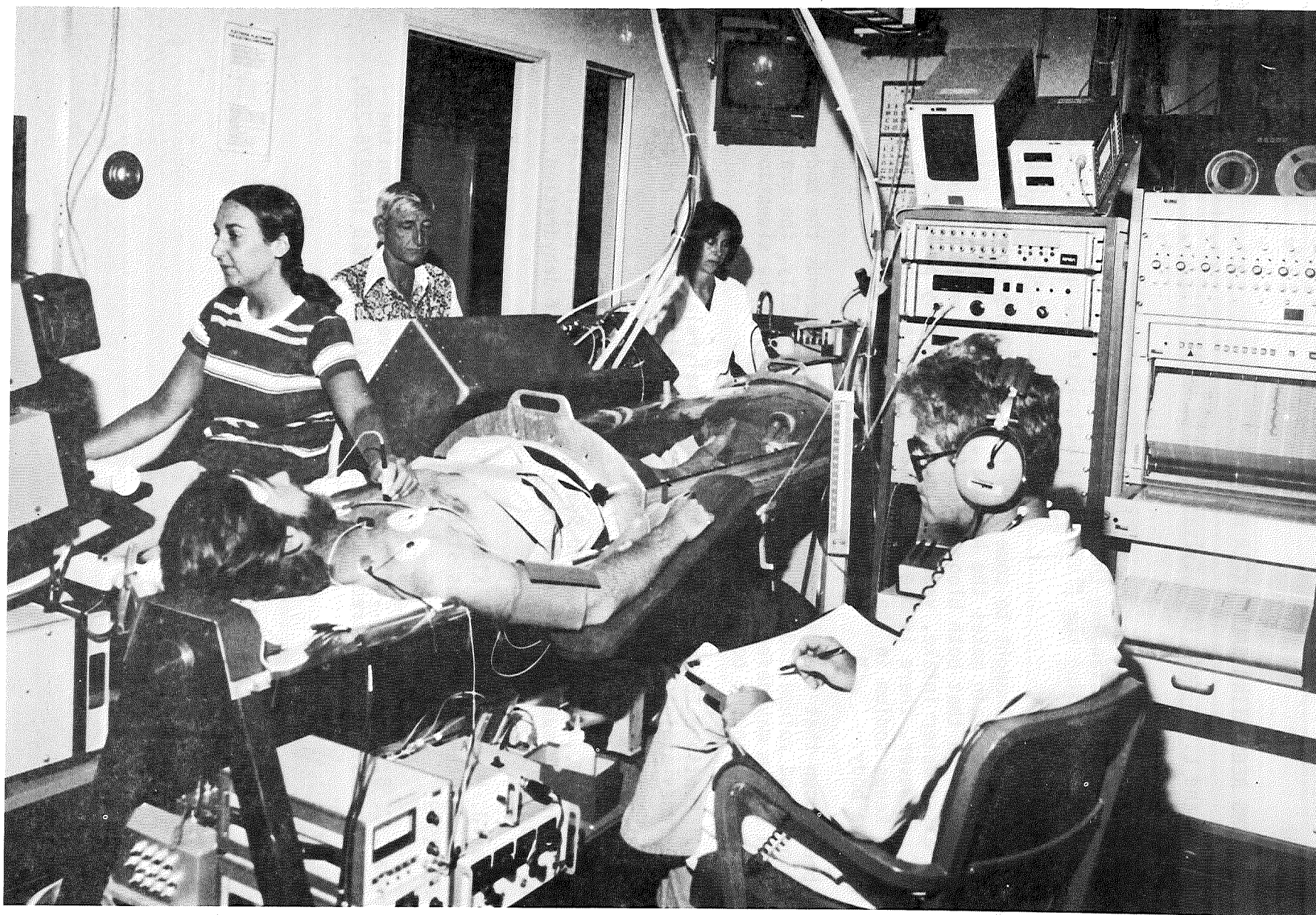
Angiotensin was once thought to come only from the kidneys; however, it is now known that the brain makes the hormone as well. Research in this laboratory revealed that both blood-borne (kidney) and brain angiotensin cause increased water intake, vasopressin release, and sympathetic nervous discharge. However, there is one important difference: Whereas blood-borne angiotensin keeps sodium in the body, brain angiotensin increases sodium loss from the body.

It has been known that the kidney angiotensin system defends the body against low blood volume and/or body sodium. Theoretically, the brain angiotensin system may defend the body against the opposite situations, i.e., high blood volume and/or body sodium.

Studies will continue to investigate the functional relationship between brain and kidney angiotensin and their effects on salt and water balance.

PUBLICATIONS

1. Summy-Long, J., Keil, L. C., and Severs, W. B. "Identification of vasopressin in the subfornical organ region: Effects of dehydration." BRAIN RES 140:241-250, 1978.
2. Kapsha, J. M., Keil, L. C., Klase, P. A., and Severs, W. B. "Central effects of angiotensin in various state of sodium balance." PHARMACOLOGY 18:25-33, 1979.
3. Thomas, C. B., Keil, L. C., Klase, P. A., and Severs, W. B. "On the role of angiotensin in the cerebellum." PROC SOC EXP BIOL MED 160:278-280, 1979.



A bedrest subject undergoes LBNP. The horizontal chamber encasing the subject's lower body is evacuated to -50 mmHg. An echocardiographic technician is imaging his heart during this stress.

EFFECTS OF ALTERED GRAVITATIONAL STRESS ON FLUID BALANCE AND THE CIRCULATION OF BLOOD

J. A. Luetscher (Stanford University Hospital)

Bedrest studies are conducted to relate fluid and electrolyte changes to changes observed in the renin-angiotensin system and to study this system's effect on aldosterone secretion, kidney function, and vasomotor tone.

A 10-day bedrest study on twelve 44-55 year old men shows that very low recumbent plasma renin activity (PRA), which does not increase normally after LBNP, can predict poor tolerance to LBNP and standing after bedrest. Recipients of propranolol 30 minutes before arising in the morning after bedrest had less tachycardia, more stable blood pressure, and fewer symptoms of pre-syncope.

Future plans include bedrest studies to further evaluate the prediction value of PRA for LBNP tolerance and the beneficial effects of propranolol. The role of certain vasodilators in fluid balance and circulatory changes after bedrest will also be investigated.

PUBLICATIONS

1. Zager, P. G., Luetscher, J. A., Hsueh, W. A., Chavarri, M. R., and Dowdy, A. J. "Adrenocorticotropin-stimulated secretion of aldosterone and cortisol, computed from plasma and red blood cell measurements." J CLIN ENDOCRINOL METAB 48:441, 1979.
2. Zager, P. G., Hsueh, W. A., Luetscher, J. A., Biglieri, E. G., and Dowdy, A. J. "Effect of des-asp¹-angiotensin II on secretion and metabolism of aldosterone." J CLIN ENDOCRINOL METAB 50:874, 1980.

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RENAL RECEPTORS AND SIMULATED WEIGHTLESSNESS

E. M. Holton (NASA-ARC)

Fluid and electrolyte balance may be changed by altered hormone levels. According to another hypothesis, the balance may be changed by an altered target-tissue sensitivity to any given level of hormone. Resistance to glucocorticoid action in individuals during stress supports this latter view. Changes in hormone receptors in target tissue may contribute to altered response to both mineralocorticoid and glucocorticoid administration during various hormonal or metabolic states.

To study modifications of receptor regulation or related mechanisms, rats exposed to cold (4°C) for 5, 10, or 15 days were compared with harnessed rats suspended for similar periods of time. Glucocorticoid values suggested that suspended rats were no more stressed than pair-fed controls, whereas cold-stressed rats had significantly elevated steroid levels.

Cold-stress and harness experiments will be repeated for longer periods. Other classical stress situations in rats will determine whether receptor modulation occurs as expected with changes in steroid levels.

PUBLICATIONS

None

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HORMONAL CONTROL OF BLOOD VOLUME

D. S. Gann (Rhode Island Hospital)

Methods by which plasma volume loss can be restored are being investigated. Preliminary experiments in dogs suggest that restitution of blood volume is delayed if the animal is in the head-down position. The levels of hormones that facilitate restitution do not change, perhaps because atrial and carotid receptors remain stimulated in the head-down position.

Glucagon infusions facilitate restoration of blood volume after hemorrhage. Future research efforts include determination of glucagon secretion rate in horizontal and head-down animals.

PUBLICATIONS

1. Engeland, W. C., Dempsher, D., Byrnes, G. J., Presnell, K., and Gann, D. S. FED PROC 38:982, 1979.

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7. RADIATION EFFECTS AND PROTECTION

UPN	PI	SHORT TITLE
199-20-71-01	Benton	Analysis of HZE Particle Dose
199-20-71-02	Wood	Chronic Radiation Effects
199-20-71-03	Ainsworth	Biomedical Effects of HZE
199-20-71-08	Braby	Universal Dosimeter Feasibility
199-20-71-10	Lett	Fibroblast Viability
199-20-72-02	Miquel	Space Radiation on Nerve Tissue Cells
199-20-72-03	Philpott	Cell Tissue Particle Track Location
199-20-72-06	Kraft	Radiation Effects of HZE Particles
199-20-76-01	Wilson	Radiation Protection Methods

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INTRODUCTION

The biological effects of ionizing radiations of solar and galactic origins and those found in radiation belts are the subject of this RTOP. Of particular concern are the heavy high-energy particles, or HZE particles, found only in space, especially at geosynchronous orbit or during deep-space manned missions. Only recently has it been possible to reproduce HZE-particle radiation on Earth. Previous studies had been limited to irradiation on balloons or in satellites.

The potential hazards of HZE particles received increased attention after crew members of Apollo 11 and subsequent missions reported "light flashes" occurring once or twice per minute during periods of dark in the spacecraft. These "streaks," "clouds," or "supernovae" seemed to be the direct interaction of HZE particles with cells of the visual nervous system.

A series of experiments aboard Apollo 16 and 17 sought to identify the effects of HZE particles on life forms of varying complexity (e.g., protozoa, plant embryos, simple-animal eggs). Findings included changes in cellular and organic growth, damages to cell nuclei and other subcellular systems, and significant genetic mutations.

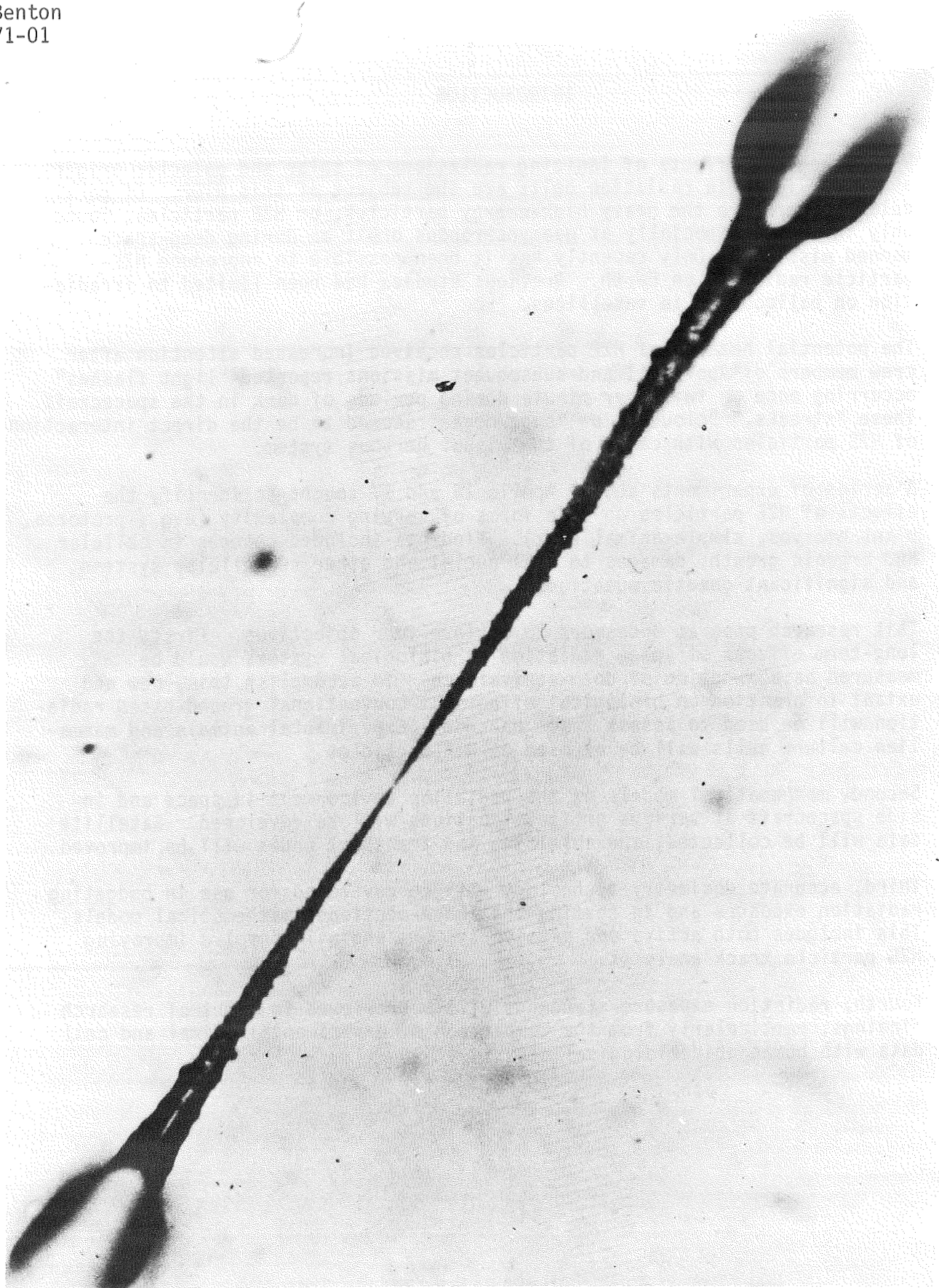
This research program endeavors to achieve four objectives. First, the long-term effects of space radiation on biological systems would be measured as a function of dose-equivalence. To accomplish this, new and extant information on biological effects of conventional ground-based radiation will be used to assess space hazards. Experimental animals and mammalian culture cells will be exposed to HZE particles.

Second, mathematical models of the radiation environment in space and inside spacecraft at various orbital locations will be developed. Satellite data will be collected, and shielding and transport codes will be improved.

Third, accurate dosimetry technology will be developed for use in budgeting radiation exposure and in testing the above-mentioned mathematical models. This includes both active and passive systems and will involve improving HZE particle track analysis.

Fourth, radiation exposure standards will be reviewed in light of research findings, particularly from the comparison of experimental animal and cell data with human epidemiological data.

Benton
71-01



Photomicrograph of an HZE particle track in plastic nuclear track detector. The length of the track reflects the radiation damage produced by the HZE particle in tissue-equivalent material. The number density of these tracks is a measure of dose received by astronauts while in orbit.

ANALYSIS OF HZE PARTICLE DOSE

E. V. Benton (University of San Francisco)

The purpose of this project is to develop the accurate dosimetry that is so vital for measuring radiation exposure in spacecraft and in ground-based experiments. Accuracy is particularly important since the deposited dose changes according to each ion and its velocity.

Results of dose distribution and other studies are now being applied to biological tissues being exposed at Berkeley accelerators and on Cosmos spacecraft.

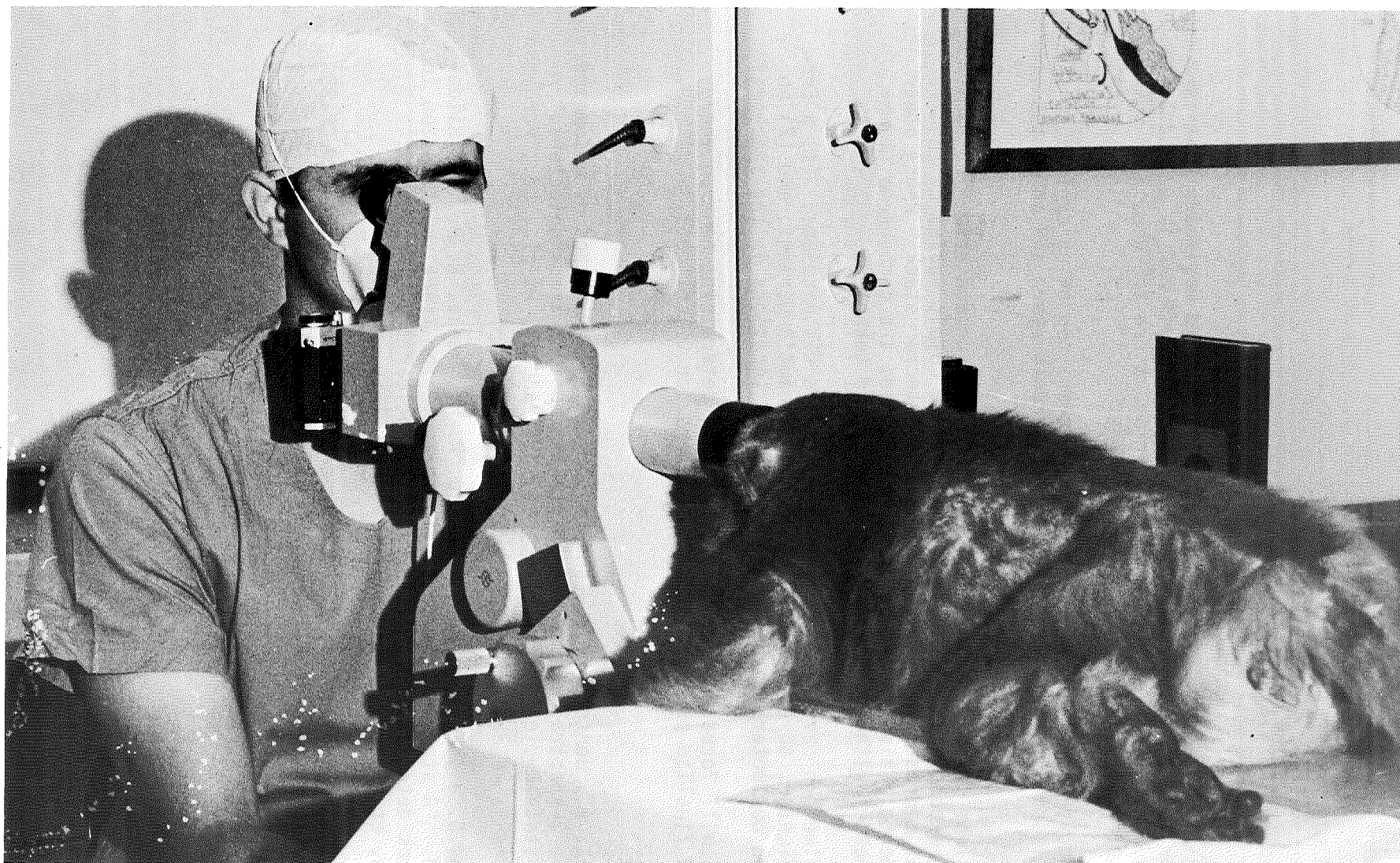
Passive nuclear track detector materials that have proven effective for determining exposure to high-energy, high-charge cosmic radiation require manual light microscopy of each plate in the detector stack. Among other accomplishments, this research effort has improved the cumbersome, time-consuming method with an automated image analysis technique.

Passive dosimeters have been designed for Shuttle OFT missions: (1) a Crew Passive Dosimeter, to be attached to each astronaut's garment, and (2) an Area Passive Dosimeter, to be stowed on various locations in the spacecraft.

The project will focus on improving methods of determining neutron energy spectra and finalize preparation of dosimeters for OFT flights.

PUBLICATIONS

1. Henke, R. P., Benton, E. V., and Cassou, R. M. "A method of automated HZE-particle Z-spectra measurement in plastic nuclear track detectors." In: Solid State Nuclear Track Detectors, H. Francois, et al., ed., Pergamon Press, NY, 1980, pp 509-516.
2. Johnson, D. J., Benton, E. V., Cassou, R. M., Henke, R. P., and Hildebrand, D. J. "A study of the critical dip angle for track registration in plastic track detectors." In: Solid State Nuclear Track Detectors, H. Francois, et al., ed., Pergamon Press, NY, 1980, pp 303-310.
3. Cassou, R. M. and Benton, E. V. "Properties and applications of CR-39 polymeric nuclear track detector." NUCL TRACK DETECT 2:173-179, 1978.



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Long-term effects of radiation. The monkey is having his eye examined with a funduscope capable of photographing the interior of the eye. This type of examination is carried out annually to detect any visible ocular effects of radiation, especially cataracts.

RADIATION EFFECTS OF MANNED SPACEFLIGHT

D. H. Wood (USAF School of Aerospace Medicine)

Initiated in 1964, the objective of this research was originally to evaluate the acute effects of exposure to particulate radiation (i.e., proton radiation). A colony of rhesus monkeys were exposed to various types of radiation at different dose levels. The task is now devoted to the assessment of chronic delayed biological effects of those exposures.

In 1965, 217 rhesus monkeys that survived acute whole body proton irradiation were banded together, along with 33 of their controls, to form the Chronic Radiation Colony. Fifteen years of postradiation findings indicated radiation-related lifespan shortening, increased incidence of malignant tumor formation, and the formation of cataracts.

Even though these observations are currently limited to those monkeys in the colony that received more than 250 rad of proton radiation, they clearly reflect the possibility of delayed effects in man. Continued surveillance of the colony as the subjects grow older will determine if similar radiation-related effects occur in the lower (25 to 113 rad) dose groups.

PUBLICATIONS

1. Casey, H. W., Coogan, P. S., and Traynor, J. E. "Late effects of 32 MeV proton irradiation in primates." RAD RES 39:634-642, 1968.
2. Haymaker, W., Sturrock, D., Kirk, J. H., Casey, H. W., and Call, N. A. "Neuropathological evaluation of monkeys exposed to body alone X-irradiation." SPACE LIFE SCI 3:210-225, 1972.
3. Krupp, J. H. "Nine-year mortality experience in proton-exposed Macaca mulatta." RAD RES 67:244-251, 1976.



Effects of high Linear Energy Transfer (LET) radiations. LET radiations of space cause increased incidence of tumors. Illustrated here is harderian gland tumor and mammary tumor (insert).

BIOMEDICAL SIGNIFICANCE OF HIGH ENERGY MULTI-CHARGED COSMIC RAYS FOR
CANCER INDUCTION AND MUTATION

E. J. Ainsworth (University of California, Berkeley)

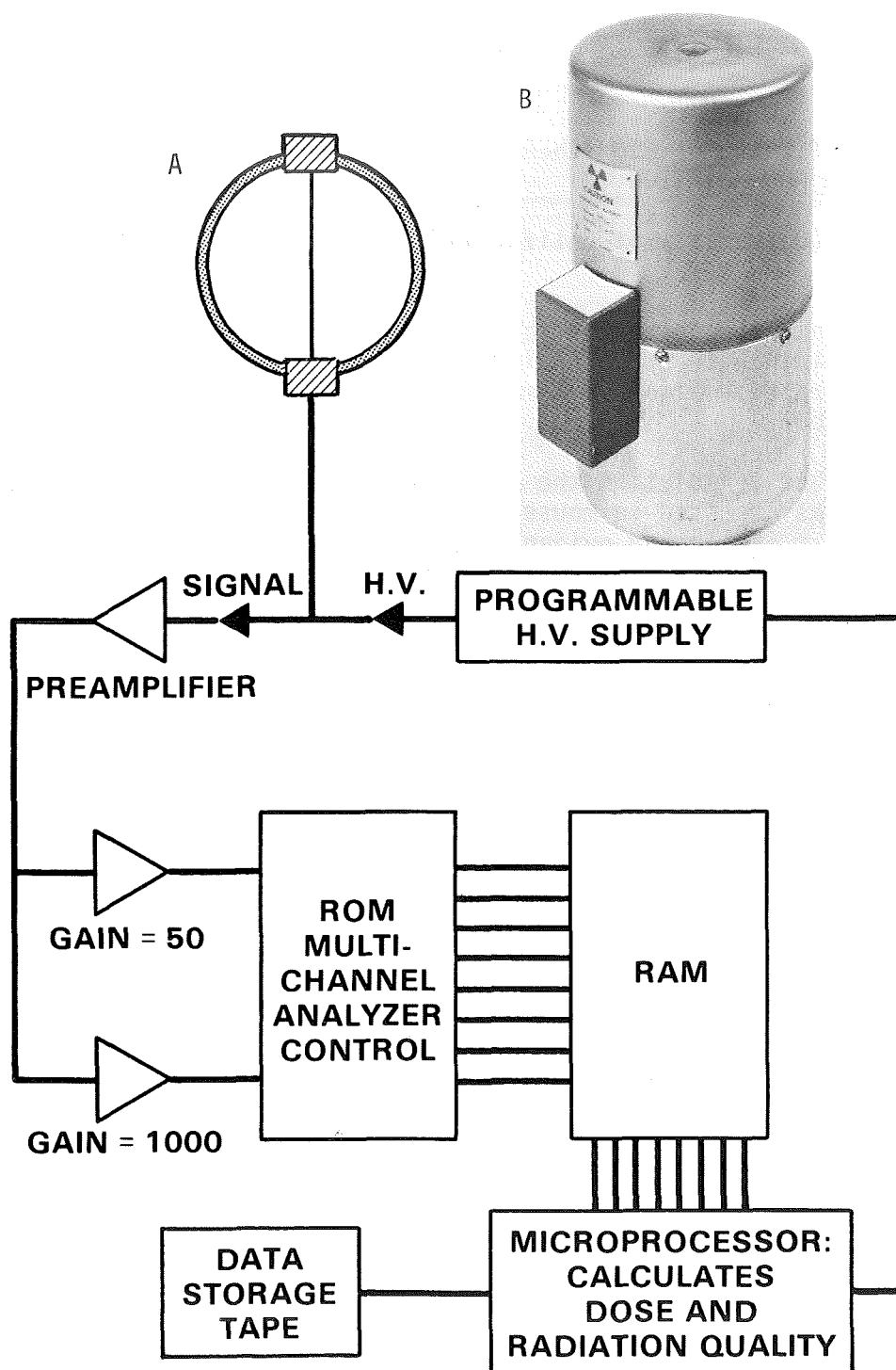
The Bevalac, a unique accelerator facility that produces high energy HZE particle beams similar to space radiation, is being used to study mutation and neoplastic transformation in mammalian cell cultures and life-span shortening in mice.

Within six weeks of irradiation the frequency of mutations or neoplastic transformation was assessed in mouse cells. Although these studies are at an early stage, it is already evident that neon particles produce four times as many deletion mutations as X-rays. Likewise, carbon and neon particles induce many more neoplastic transformations than do X-rays. The determination of reliable risk estimates requires further work.

Mortality data and records of autopsies and tumor types are being collected on mice exposed to carbon, neon, or argon particles.

PUBLICATIONS

1. Yang, T. C., Tobias, C. A., Blakely, E. A., Craise, L. M., Madfes, I. S., Perez, C., and Howard, J. "Enhancement effects of high-energy neon particles on the viral transformation of mouse C3H10T1/2 cells in vitro." RAD RES 81: 208-223, 1980.



Real-time Active Dosimetry System. The dose actually received by small objects exposed to a uniform radiation field varies according to the interactions between radiation and matter. A spherical proportional counter (A) sealed in a chamber (B) filled with gas at low pressure is used to simulate the nucleus of a cell. Two analog-to-digital converters record the data to account for the wide dose variation produced by individual charged particles: Read Only Memory (ROM) adds a count to the appropriate channel of a Random Access Memory (RAM) for each particle detected. The microprocessor automatically calculates the dose, dose rate, and radiation quality from the stored distribution. It will also turn on a calibration source, determine the position of the resulting peak in the spectrum, and adjust the high voltage supply to keep the instrument in calibration.

FEASIBILITY STUDY OF AN ACTIVE UNIVERSAL DOSIMETER FOR SPACE RADIATION ENVIRONMENT

L. A. Braby (Battelle Pacific Northwest Laboratories)

In this new project, a real-time active dosimetry system will be developed that can measure both instantaneous and accumulated dose (rads) and dose-equivalent (rems) from all types of space radiation.

Results will be displayed in such a way that they can be employed in making decisions regarding radiation protection and so that they can be recorded along with basic energy deposition data.

Spherical proportional counters similar to those used for microdosimetry research studies will be developed for use in space. Alternative methods of determining radiation quality from the physical data will be studied.

PUBLICATIONS

None

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FIBROBLAST VIABILITY

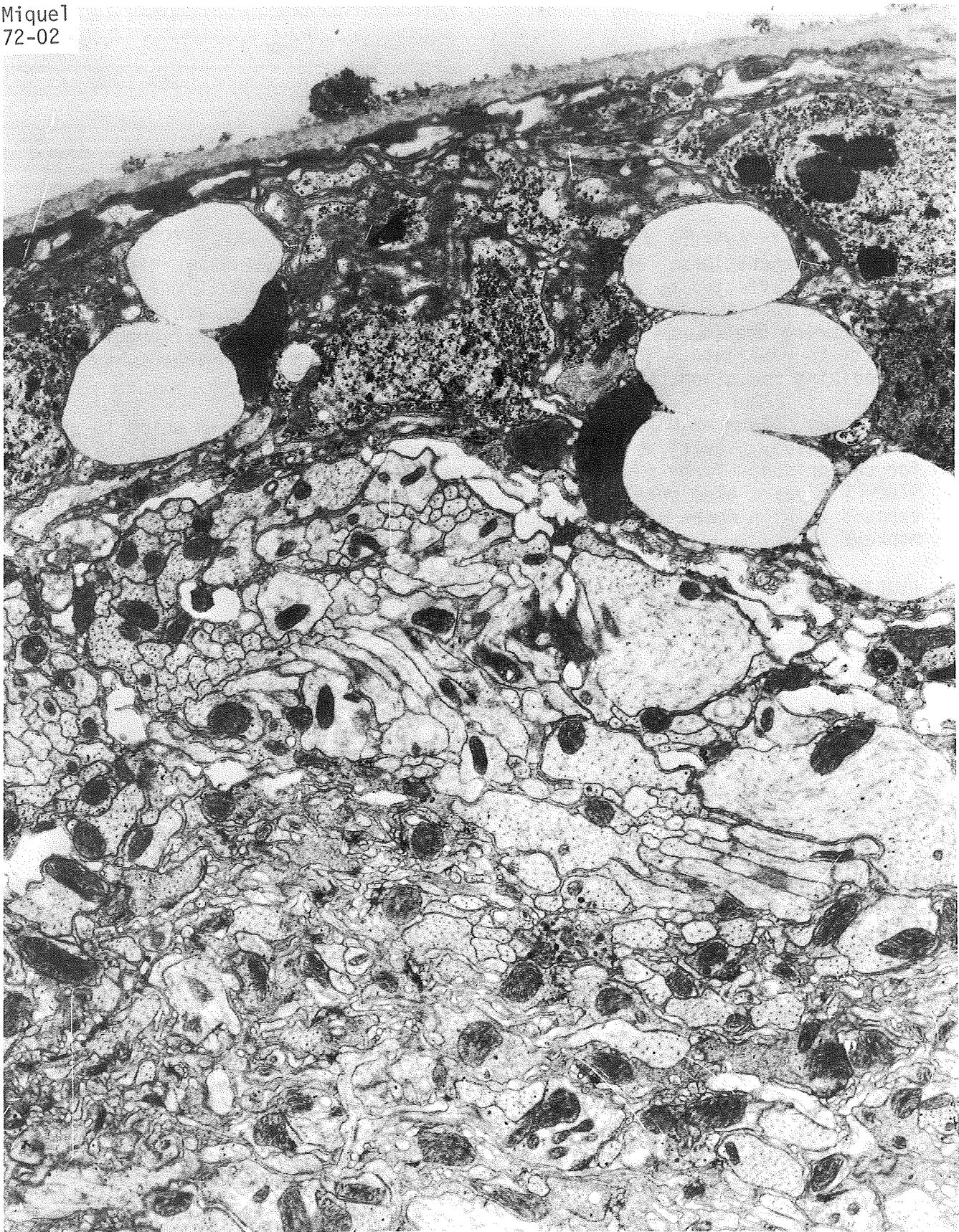
J. T. Lett (Colorado State University)

Fibroblasts in culture demonstrate a capability to go through only a limited number of generations. This number of generations, or viability, has been shown to be affected by both the age of the organism from which the fibroblasts are obtained and exposure to ionizing radiation. Presumably, mutations occur during the course of the organism's life which reduce the fibroblasts' ability to replicate. This natural process is quickened by mutagens, such as ionizing radiation, which accelerate the aging process.

The monkey colony at USAF/AMD represents a unique resource with which to pursue this study. Relatively old exposed and control monkeys are available for comparison. Young monkeys are also available for comparison with the older (15 years old) ones. The initial study will compare a group of animals exposed to high doses of proton radiation with aged controls and with young monkeys.

PUBLICATIONS

None



Effects of space radiation on nerve tissue cells. Cephalic ganglionic center ("brain") of an adult fruit fly at 35 days after exposure to approximately 1 hit/cell of krypton. Note two areas of "columnar" cystic degeneration induced by direct injury to nerve cells by HZE particles. (X14,000)

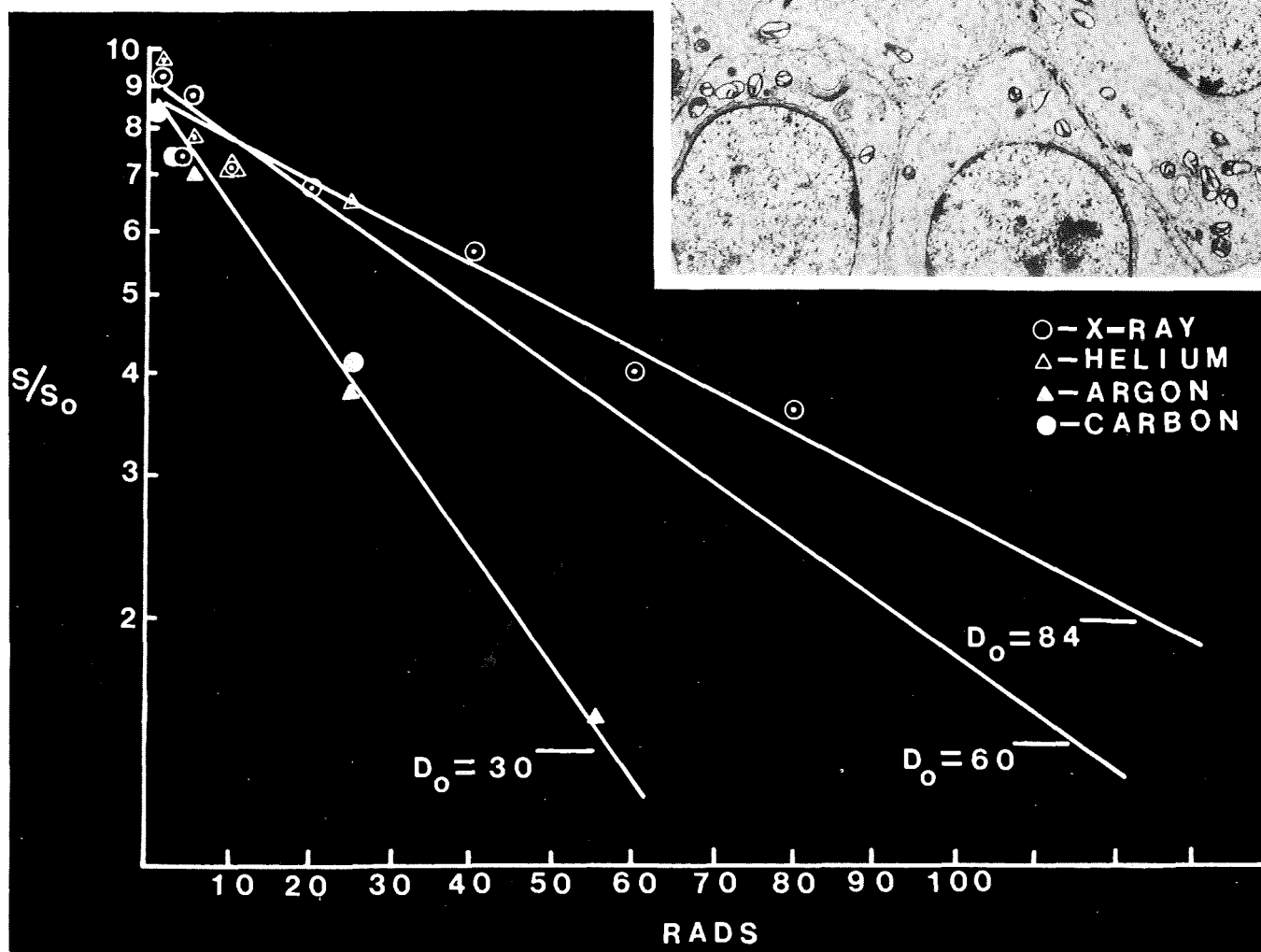
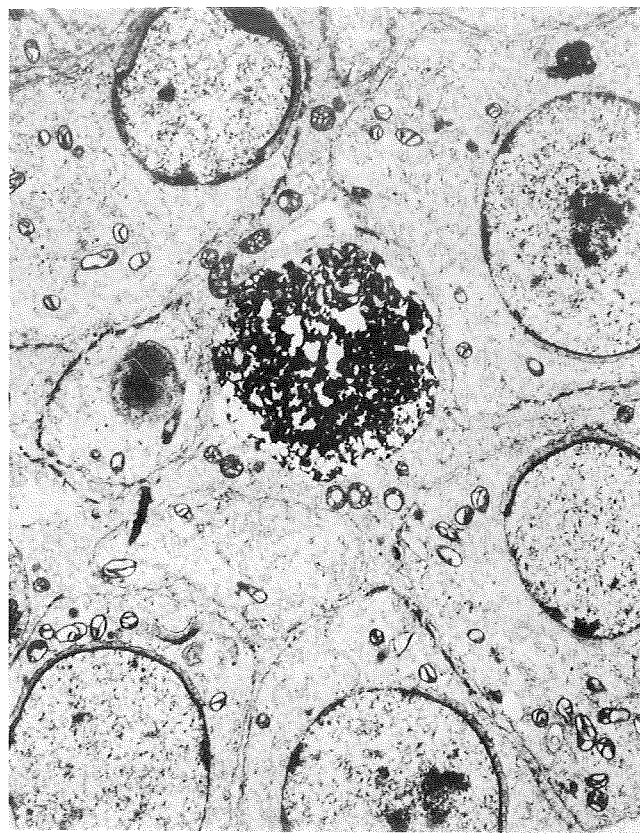
EFFECTS OF HEAVY PARTICLE RADIATION ON NERVE CELLS

J. Miquel (NASA-ARC)

The brain of a fruit fly is ideal for studying the direct effects of particle radiation since it is devoid of blood vessels. One electron microscopic investigation of the brain of irradiated flies revealed that brain injury results from single hits of heavy particles. More specifically, morphological alterations in nerve cells and changes in the structures responsible for energy production (mitochondria) in nerve and glial cells were observed.

PUBLICATIONS

None



Irradiation effects on testis cells. The micrograph shows the effect of ten rads of neon particles 3 days after irradiation of mouse testis. Note the necrotic (dying) cell in the center, surrounded by normal cells. The graph indicates the extent of damage by specified particles (S/S_0 = fraction of cells surviving irradiation; D_0 = slope = dose required to kill 37% of the cells).

RADIATION-INDUCED EFFECTS IN CELLS AND TISSUES AND PARTICLE TRACK LOCATION

D. E. Philpott (NASA-ARC)

Cosmic rays are known to pass through the walls of the spacecraft and its occupants during space missions. Astronauts have seen light flashes during translunar and orbital flights even with their eyes closed, thus providing additional evidence that the cosmic rays come through the spacecraft and penetrate the retina. Recently, cellular alterations and cell loss in the retina of rats flown on two Cosmos satellites have been demonstrated.

Studies thus far show that testis cells are also very sensitive to cosmos radiation. They are damaged by doses as low as one rad and, perhaps, as low as 0.1 rad. Sensitivity to low doses of heavy ions seems to differ slightly among populations of testis cells.

Dose-response relationships of HZE particles and testis germ cells and retinal cells will be characterized. Cell alterations and kinetics will also be investigated.

PUBLICATIONS

1. Philpott, D. E., Corbett, R., Turnbull, C., Harrison, G., Leafer, D., Block, S., Sapp, W., Klein, G., and Savick, L. "Cosmic ray effects on the eyes of rats flown on Cosmos No. 782 experiment." AVIAT SPACE ENVIRON MED 51(6):556-562, 1980.
2. Philpott, D. E., Corbett, R., Turnbull, C., Black, S., Payhoff, D., McGourty, J., Lee, R., Harrison, G., and Savick, L. "Retinal changes in rats flown on Cosmos 936: A cosmic ray experiment." AVIAT SPACE ENVIRON MED 51(6):556-562, 1980.
3. Malachowski, M. J., Philpott, D. E., and Corbett, R. "Retinal tissue-response to accelerated iron nuclei." RAD RES 83(2):472-3, 1980.



Brain tissue from a normal mouse. A region between nerve cell bodies is shown. Here, nervous impulses are transmitted from nerve cell to nerve cell. The structures are very well organized. (X40,000)



A similar region in a mouse irradiated with argon particles. Note how the organelles have shrunk and been disrupted. The tissue has assumed a markedly disorganized aspect. (X40,000)

DIRECT AND ABSCOPAL RADIATION EFFECTS OF HZE PARTICLES

L. M. Kraft (NASA-ARC)

In this project, the head or whole body of rodents is exposed to HZE particles produced in the Bevalac of the Lawrence Berkeley Laboratory. Microscopic sections of the brain are being examined from a few minutes to 2-3 years after irradiation. Particular emphasis is placed on injury to nerve cells and to more numerous neuroglia, or supporting cells of the brain.

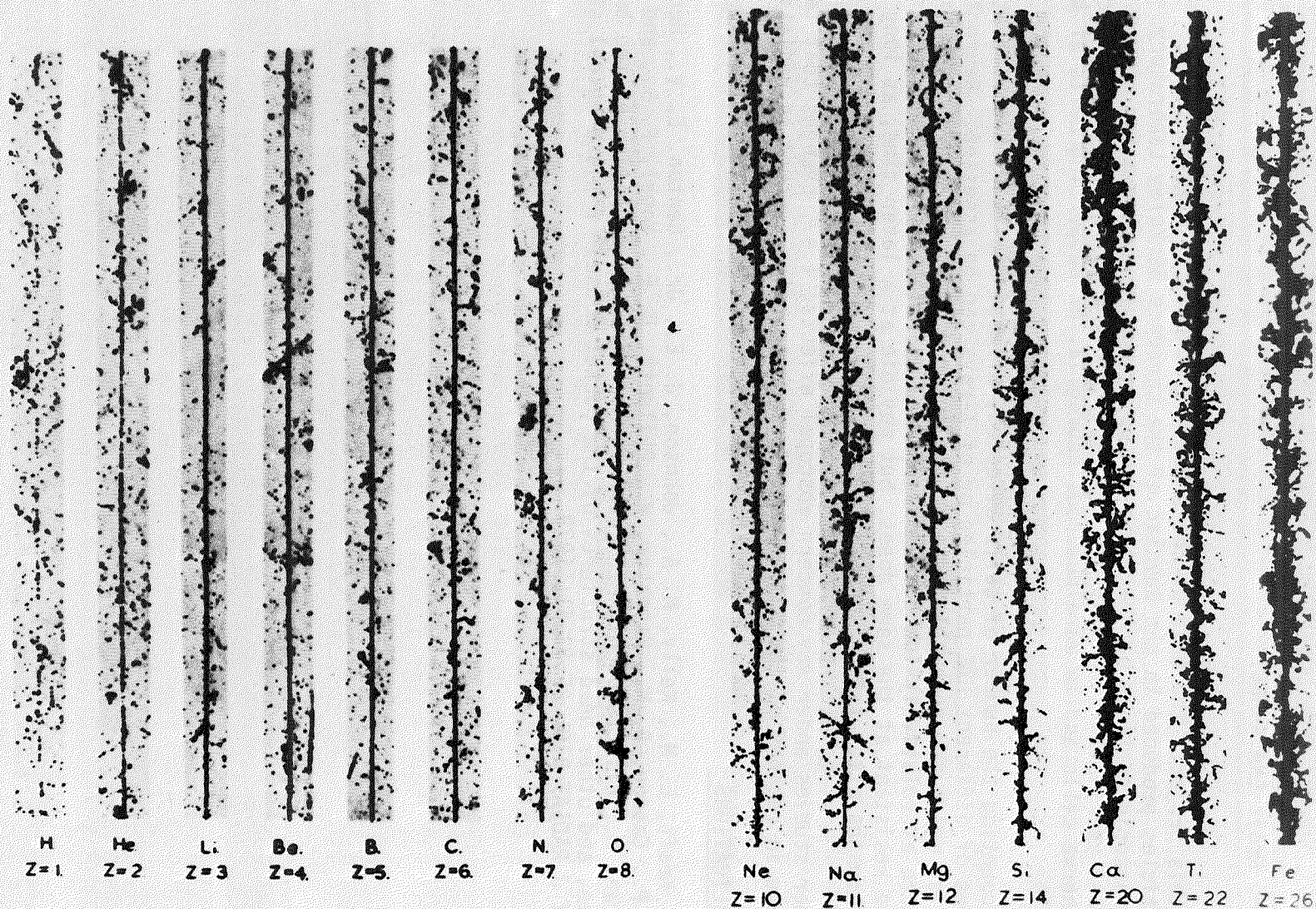
By counting the number of cells affected, effects due to various radiation doses of different HZE particles or of X-rays can be assessed. Neuroglial cells, which are renewable, die or are injured within 48 hours after exposure at relatively low doses. Nerve cells, which are not renewable, are more resistant at the same doses, but may die at a later time, as long as 1-6 months after irradiation.

Other studies under way concern abscopal effects, i.e., changes that take place in regions of the body remote from those being exposed to radiation.

PUBLICATIONS

1. Kraft, L. M., Kelly, M. A., Johnson, J. E., Jr., Benton, E. V., Henke, R. P., Cassou, R. M., Haymaker, W., Philpott, D. E., Vogel, F. S., and Zeman, W. "Effects of high-LET neon (^{20}Ne) particle radiation on the brain, eyes, and other head structures of the pocket mouse: A histological study." INT J RADIAT BIOL 35:33-61, 1979.

COSMIC RAY ION TRACKS IN NUCLEAR EMULSION



RADIATION PROTECTION STUDIES AT THE LANGLEY RESEARCH CENTER

J. W. Wilson (Langley Research Center)

Of concern in this effort are the basic physics of the interactions between space radiation and materials and biological systems with an aim toward improved methods of shielding and monitoring of the astronaut's environment. Experiments on interaction mechanisms should facilitate the development of mathematical models of the mechanisms. The need for adequate shielding is complicated by the minimal weight allowance.

The main problem to be investigated in this new project concern:

- 1) Various shield configurations and compositions called for by the accumulated exposure to galactic heavy ions over the astronaut's career;
- 2) Temporary shelters required during short-term fluctuations of the outer zone radiations and during solar particle events;
- 3) Protection requirements during extravehicular activity;
- 4) Radiation doses related to biological and systems response; and
- 5) Relationships between dosimetric quantities and actual doses received by body organs.

PUBLICATIONS

1. Wilson, J. W. "Measurements of the inclusive neutron production by relativistic neon ions on uranium." PHY REV L 43:1985, 1979.
2. Wilson, J. W. "Methods of shield analysis for protection against electrons in space." NUCL TECH 35:178, 1977.

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8. HUMAN BEHAVIOR AND PERFORMANCE

UPN	PI	SHORT TITLE
199-20-82-01	Winget	Human Biorhythms
199-20-82-02	Brady	Small Group Response to Stress
199-20-82-03	Helmreich	Crew Selection Methods

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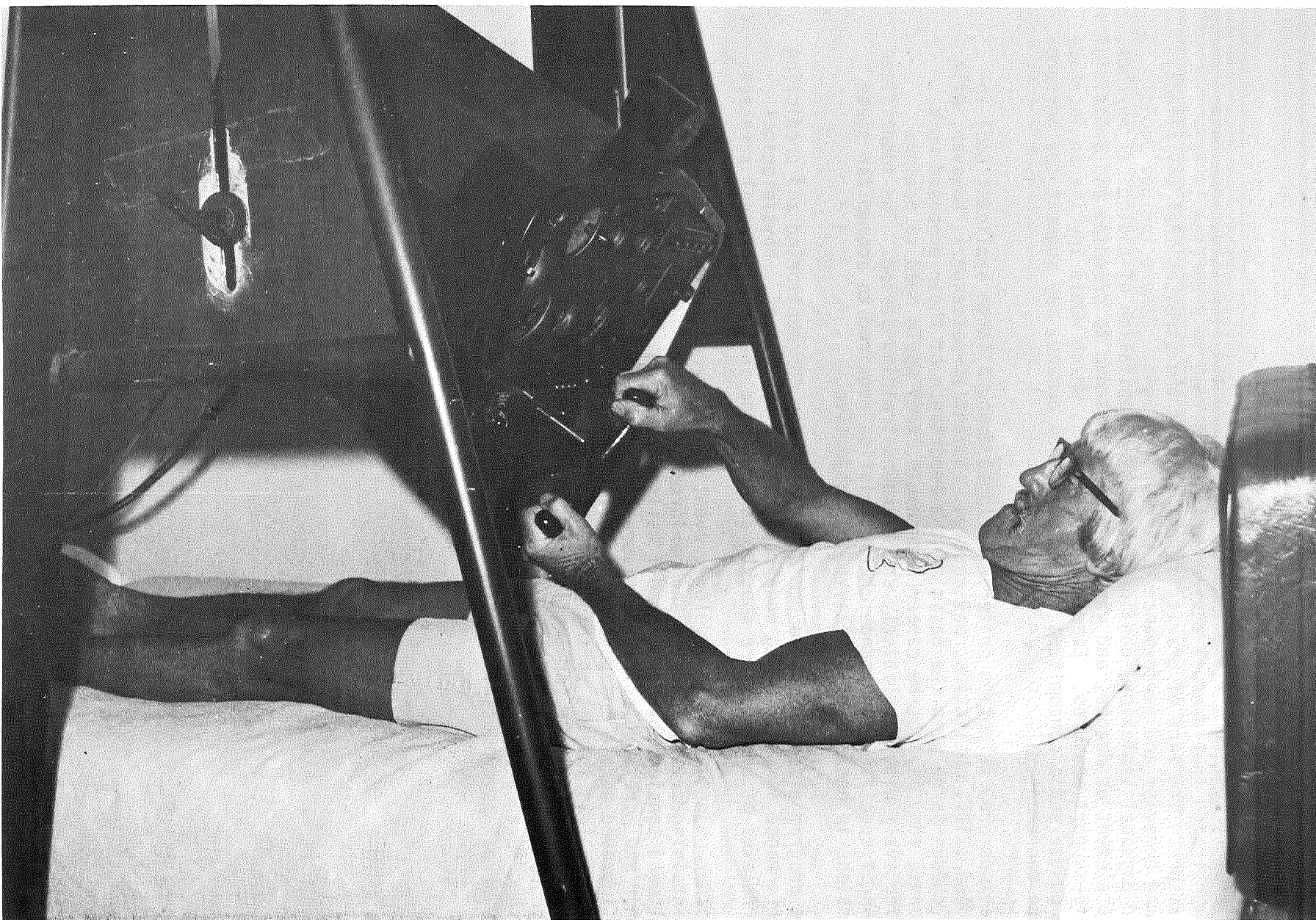
INTRODUCTION

Laboratory research, field studies, and documented life situations have demonstrated that unusual environments often lead to a decline in performance. The lack of gravity is only one of the stresses that may affect human behavior and performance during spaceflight. Others include social and physical isolation, confinement, desynchronization of biological rhythms, the element of danger, and various discomforts due to crowding and artificial life-support measures. Emergency conditions, which would involve an increase in danger and a concomitant increase in task demand, may augment the performance decrement.

Previous crew selection criteria employed among a large applicant pool included skill, motivation, and courage. Scientist-passengers, however, will be chosen largely on the basis of the importance of their proposed work. Because they may not be career astronauts, they would need to perform effectively with a relatively short ground-training period. The identification of specific performance characteristics required to accomplish space missions is necessary to achieve this objective.

The program also strives to perfect techniques for monitoring and predicting performance and well-being under spaceflight conditions. Physiological correlates of behavior are sought, as are those for interpersonal stresses.

Another objective is to develop preventive or corrective procedures for maintaining crew well-being and performance. The men of the Skylab missions relieved tensions by bouncing off walls or turning somersaults in space. Other and more sophisticated leisure-time activities may contribute greatly to improved morale and performance effectiveness. An interesting observation that may lend insight to this matter is that the Skylab III crewmembers, who stayed in flight for the longest duration (84 days) yet were the most obscure to the public eye, were also the most contrary and difficult to work with. Further studies of cost vs. rewards involved in long-term space flight may reveal psychosocial solutions to the problem.



Performance testing of bedrest subject. The subject is undergoing performance testing of internal desynchronization during bedrest. He is being tested on the ATC-510, a general aviation simulator, in front of him.

HUMAN BIORHYTHMS: PERFORMANCE AND PHYSIOLOGICAL DECONDITIONING IN WEIGHTLESSNESS

C. M. Winget (NASA-ARC)

Future Shuttle missions will undoubtedly require a staggered work/rest schedule. This may disrupt daily rhythms and may in turn result in deterioration of function, mood, and performance in certain individuals. The emphasis of this project is to study the effects of the space mission environment on the stability of daily physiological rhythms and the maintenance of performance capability.

In the study of a small group in isolation, transition from constant light to normal light/dark cycles disturbed the stability of daily rhythms in body temperature and heart rate. Associated with these disturbances were increased psychosomatic complaints and deteriorated sleep and performance. An individual that is a dominant early-riser type significantly altered the biological rhythm patterns of other non-dominant individuals.

Biological rhythms tended to dissociate from each other during bedrest, the nature of this dissociation and the corresponding changes in performance remaining highly variable among individuals. In a female bedrest study, the amplitude of normal body temperature correlated significantly with the degree of individual rhythm instability.

Research is continuing with the study of controlling daily biorhythms by social interaction. Also being pursued is the identification of physiological rhythmic parameters (e.g., amplitude) with which to predict and select individuals most adaptable to the Shuttle environment.

PUBLICATIONS

1. Winget, C. M., DeRoshia, C. W., and Sandler, H. "Influences of horizontal hypokinesia on performance and circadian physiological rhythms in female humans." *PHYSIOLOGIST* 22:79-80, 1979.
2. DeRoshia, C. W. and Winget, C. M. "Comparison of the effects of horizontal and antiorthostatic hypokinesia upon circadian rhythmicity in male subjects. In: A Preliminary Report of the Joint US/USSR Hypokinesia Study, Ames Research Center, Moffett Field, CA, 1979.
3. Vernikos-Danellis, J. and Winget, C. M. "The importance of light, postural and social cues in the regulation of the plasma cortisol rhythm in man." In: Advances in the Biosciences, Vol. 19: Chronopharmacology, A. Reinberg and F. Halberg, eds., New York, Pergamon Press, 1979, pp 101-106.

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SMALL GROUP PERFORMANCE AND THE EFFECTS OF BEHAVIORAL STRESS IN A PROGRAMMED ENVIRONMENT

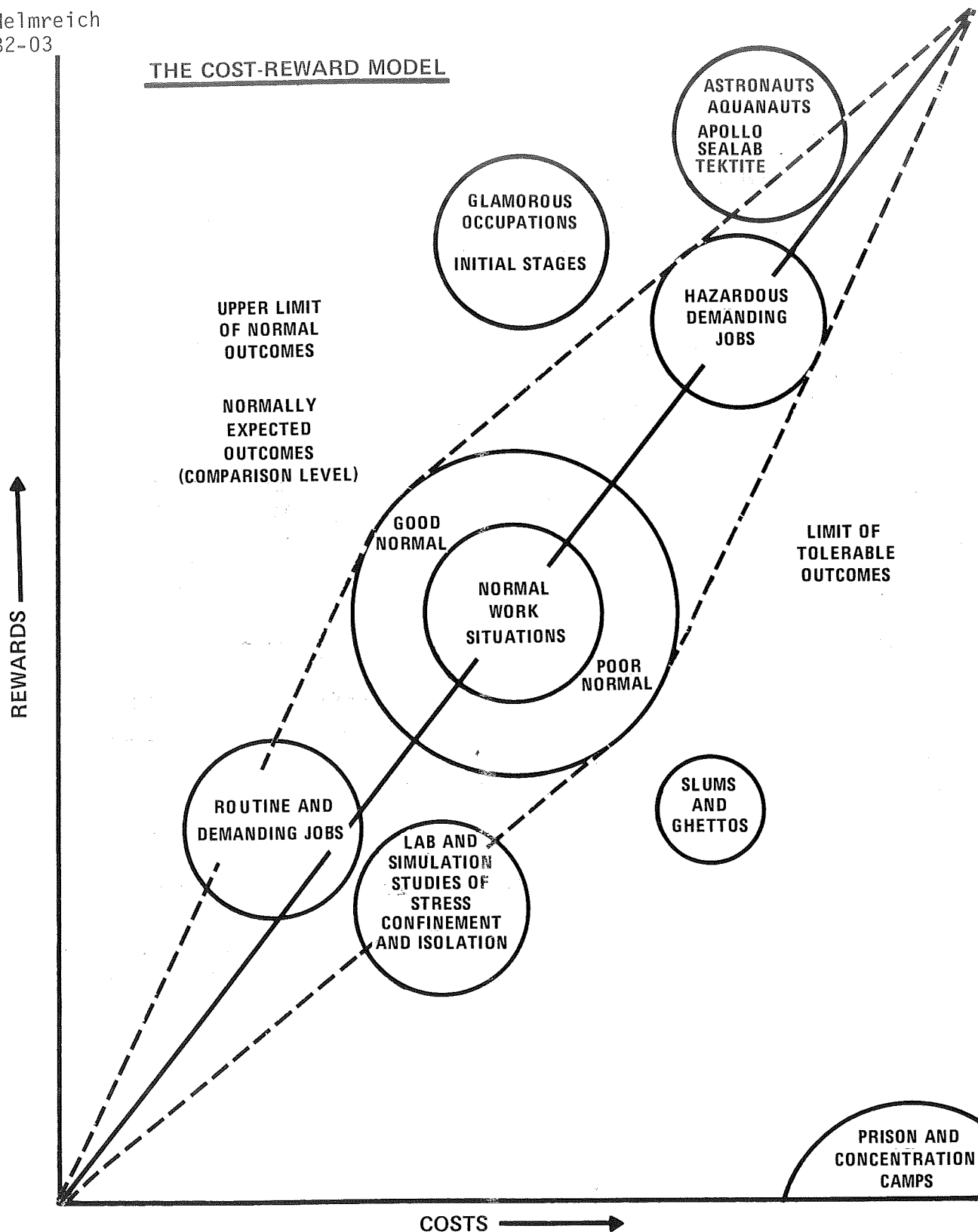
J. V. Brady (Johns Hopkins University School of Medicine)

Studies to optimize human performance and social interaction are being conducted with small groups of individuals during continual residence in a programmed laboratory. Dysphoria, interpersonal confrontation, and hostility toward the program director are observed when performance requirements are based on negative motivational forces (e.g., loss of a valued commodity or social interaction). More positive or appetitive motivational influences overcome these behavioral problems.

Recent studies on the effects on changes in group composition and organizational structures upon performance and social interaction show that established small groups resist integration of a new member into their living and work arrangements. Hormone levels measured during these experiments reveal testosterone to be particularly sensitive to changes in group composition. The direction of testosterone-level changes varies with the personalities involved.

PUBLICATIONS

1. Brady, J. V. and Emurian, H. "Behavior analysis of motivational and emotional interactions in a programmed environment." In: Nebraska Symposium on Motivation, R. Dienstbier and H. Howe, eds. University of Nebraska, 1980, pp 81-122.
2. Emurian, H., Emurian, C., Schmier, F., and Brady, J. V. "Notes on programmed environment research." JSAS Catalog of Selected Documents in Psychology, 1980, pp 81-122.
3. Emurian, H., and Brady, J. V. "Small group performance and the effects of contingency management in a programmed environment." JSAS Catalog of Selected Documents in Psychology, 9:66, 1979.



The Cost-Reward Model. The model predicts adjustment in exotic environments. Farther to the left and above the diagonal line (the absolute standard by which the individual compares options), the more desirable is the situation for a person or group. The opposite would be true for situations farther right and below the diagonal line. The dashed lines indicate the boundaries of normal attainability or tolerance. (In: Groups Under Stress, Radloff, R. & Helmreich, R., Appleton-Century-Crofts, N.Y., 1968.)

CREW SELECTION METHODS

R. L. Helmreich (University of Texas)

Drawing on research conducted on isolated groups, psychological factors that may affect performance and adjustment on future space missions have been analyzed. Problems include diminishing novelty and excitement, prolonged isolation and discomfort, greater mix of crew members, more complex multipurpose missions, and increased importance of work satisfaction and leisure needs for participants.

To this end, a major step is to define and measure personality dimensions that are expected to relate to performance and adjustment. Two personality inventories have been developed and are being validated in situations analogous to spaceflight. In one study, these inventories predicted scientific performance in a national sample of Ph.D.'s. They are also being tested on long-term bedrest subjects, both male and female, ranging in age from 25 to 65.

Other studies are being conducted using people in occupations analogous to space crews. The relationships between work and leisure satisfaction, acceptance of isolation, and personality factors are being studied among super tanker crews. Commercial airline pilots are being used to study personality and group composition as related to crew coordination and performance, particularly in emergencies. The effect of group composition on task performance and satisfaction is also being studied systematically.

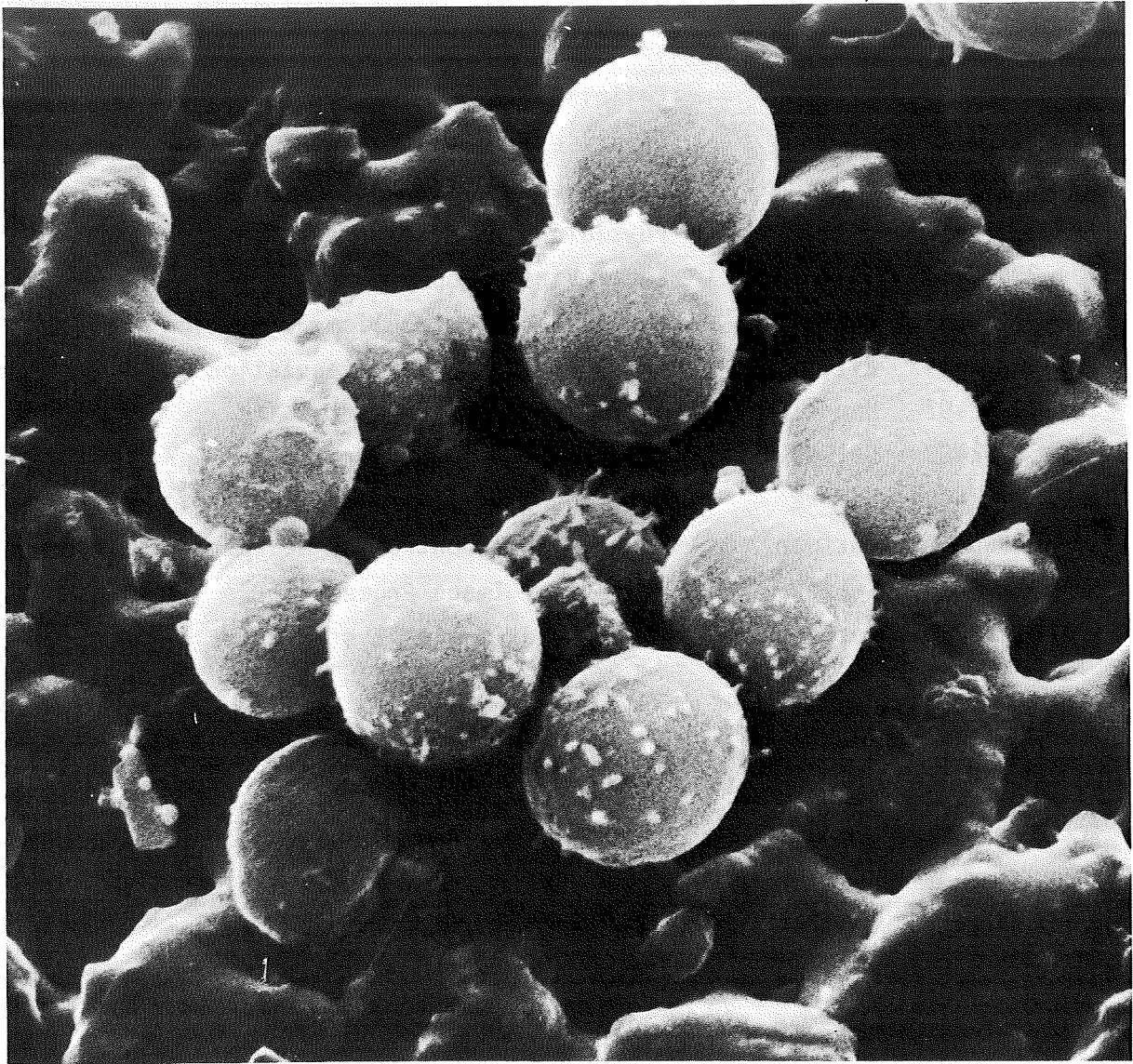
PUBLICATIONS

1. Helmreich, R. L., Wilhelm, J. A., and Runge, T. E. "Psychological considerations in future space missions." In: The Human Factors in Outer Space Production. S. Cheston and D. Winter, eds. American Association for the Advancement of Science, Washington, D.C., 1980, pp 1-23.
2. Helmreich, R. L., Spence, J. T., and Holahan, C. K. "Physiological androgyny and sex-role flexibility: A test of two hypotheses." J PERSON SOC PSYCHOL 37:1631-44, 1979.
3. Mathews, K. A., Helmreich, R. L., Beane, W. E., and Lucker, G. W. "Pattern A, achievement-striving, and scientific merit: Does pattern A help or hinder?" J PERSON SOC PSYCHOL 39:896-908, 1980.

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9. GENERAL BIOMEDICAL RESEARCH

UPN	PI	SHORT TITLE
199-20-91-01	Criswell	Cellular Immune Response
199-20-91-02	Zlatkis	Volatile Metabolites in Biological Fluids
199-20-91-04	Horrigan	Decompression Sickness
199-20-91-12	White	Physiological Systems Analysis
199-20-92-01	Tilles	Anti-Viral Prophylaxis
199-20-92-02	Dolkas	Carbohydrate Metabolism Regulation
199-20-92-04	Williams	CNS Body Temperature Regulation
199-20-92-07	Mandel	Early Disease Susceptibility
199-20-92-08	Goldsby	Monoclonal Antibody Production
199-20-92-09	Meinke	Cytofluorometric Analysis of Viral Infections
199-20-92-10	Wurtman	Nutritional Control of Neurotransmitters
199-20-94-01	Selzer	Biomedical Image Processing
199-20-94-02	Hestenes	Ultrasound Imaging System



Scanning electron micrograph of lymphocytes, which are the primary cells studied for cellular immune function in the early detection of disease program.

EARLY DETECTION OF DISEASE PROGRAM: EVALUATION OF THE CELLULAR IMMUNE RESPONSE

B. S. Criswell (Arizona Health Sciences Center)

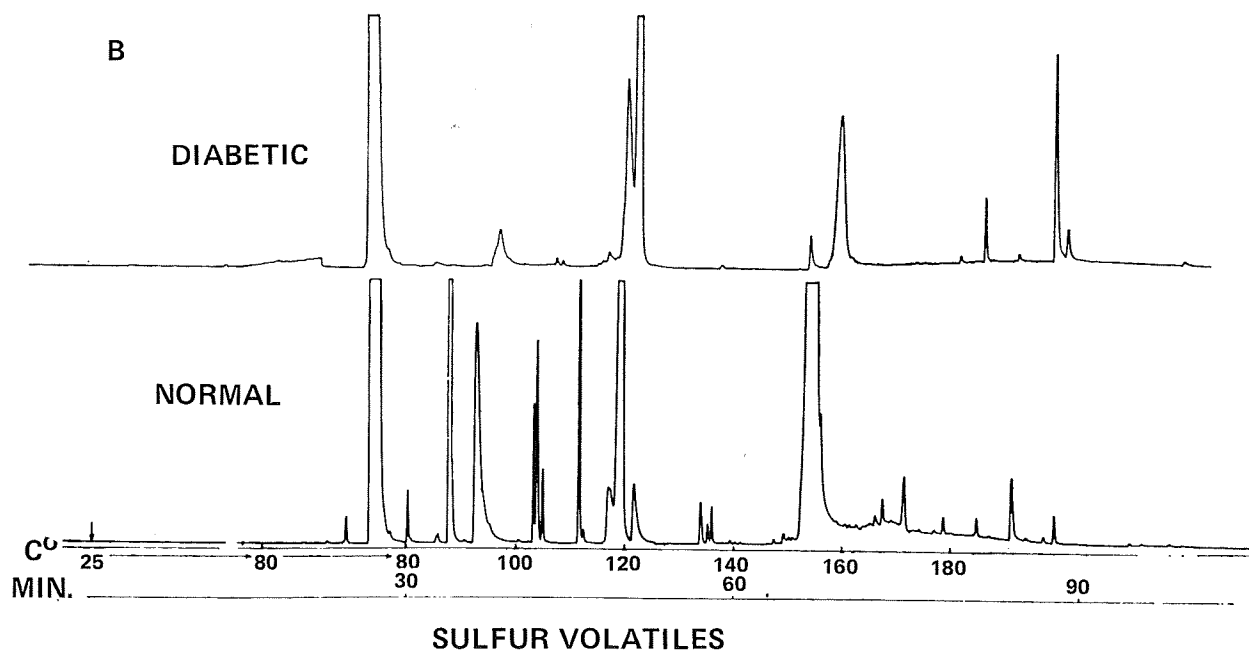
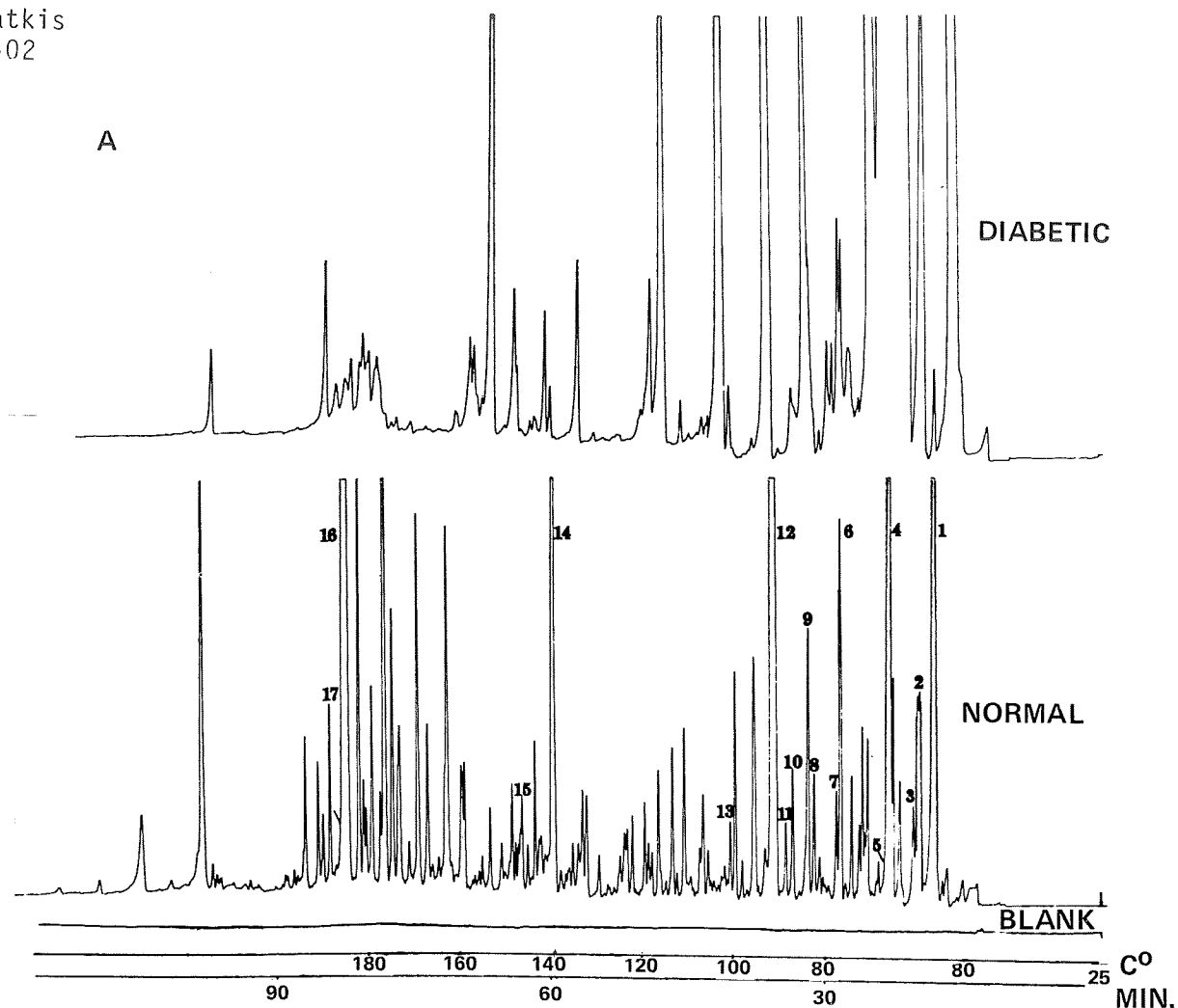
Techniques are being explored for the early detection and diagnosis of respiratory infections in their pre-clinical, asymptomatic stages. A protocol composed of various tests has been developed using study groups of individuals exposed and infected with viral agents. These tests measure changes in cellular immune status which reflect the earliest response of the body to infection.

Specific tests include the quantitative classification of lymphocytes, for which new methodologies have been developed. Studies have also been completed on cortisone- and drug-induced immunosuppression and on lymphocyte cytotoxicity.

Recently, baseline data using this protocol were obtained from normal astronauts and compared to non-astronauts' baseline values. The astronauts had significantly lower baseline values. A possible explanation for this observed difference is the astronauts' participation in physical conditioning programs. Current research involves the application of the protocol to a group of individuals undergoing exercise programs similar to those of astronauts.

PUBLICATIONS

1. Wardlow, M. L., Criswell, B. S., South, M. A., and Defazio, S. R. "Abnormal immunoglobulins in severe combined immunodeficiency -- analysis by immunoelectrophoresis and SDS-polyacrylamide gel-electrophoresis." EXP HEMATOL 7(3):151-61, 1979.
2. Greenberg, B. S., Criswell, B. S., Six, H. R., and Couch, R. B. "Lymphocyte cytotoxicity to influenza virus-infected cells -- response to vaccination and virus-infection. INFEC IMMUN 20(3):640-45, 1978.



Chromatogram profiles of normal and diabetic individuals.
(A) Comparison of urinary volatile organic compounds.
(B) Comparison of urinary volatile organic sulfur compounds.

ANALYSIS OF VOLATILE METABOLITES IN BIOLOGICAL FLUIDS AS INDICATORS OF PRODROMAL DISEASE CONDITIONS

A. Zlatkis (University of Houston, Central Campus)

One of the premises of molecular medicine is that every disease is associated with a change in the metabolic processes of the normal body resulting in a chemical change. Profiles of such changes in body fluids are used to identify chemical markers characteristic of viral infection and to predict susceptibility to viral infection in healthy individuals.

Highly sensitive gas chromatographic techniques using only microliters of sample fluids have been developed. The complex chromatograph profiles are analyzed by computers to differentiate between normal and virus-infected serum using a "two peak ratio method."

Capillary gas chromatographic profiles for 36 serum samples from 12 males voluntarily exposed to influenza virus were analyzed. The pattern of four peaks in the chromatograms provided the basis for a diagnosis of a viral infection (87% correct) and the prediction of virus susceptibility in a normal population prior to exposure. Viral exposure trials with mice indicate that this analytical approach easily distinguishes between infected mice and normal ones.

Future studies will increase the sample sizes of both humans and mice. Gas chromatography/mass spectroscopy will be used to identify the substances in the serum responsible for the four peaks in the viral diagnosis.

PUBLICATIONS

1. Poole, C. F., Zlatkis, A., Sye, W. F., Singhawangcha, S., and Morgan, E. O. "The determination of steroids with and without natural electrophores by gas-chromatography and electron-capture detection." LIPIDS 15(9):734-44, 1980.
2. Zlatkis, A., Lee, K. Y., Poole, C. F., and Holzer, G. "Capillary column gas chromatographic profile analysis of volatile compounds in sera of normal and virus infected patients." J CHROMATOGR BIOMED APPL 163:125, 1979.
3. Zlatkis, A., Brazell, R., Bafus, D. A., and Spencer, P. S. "Volatile metabolites in sera of normal and diabetic patients." J CHROMATOGR BIOMED APPL 182:137, 1980.

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DECOMPRESSION SICKNESS SUSCEPTIBILITY

D. J. Horrigan, Jr. (NASA-JSC)

Plans for the Shuttle program and future space efforts include extravehicular activity for crewmembers to work on the assembly and maintenance of satellites and other orbiting devices. It is necessary to protect such space workers against "the bends."

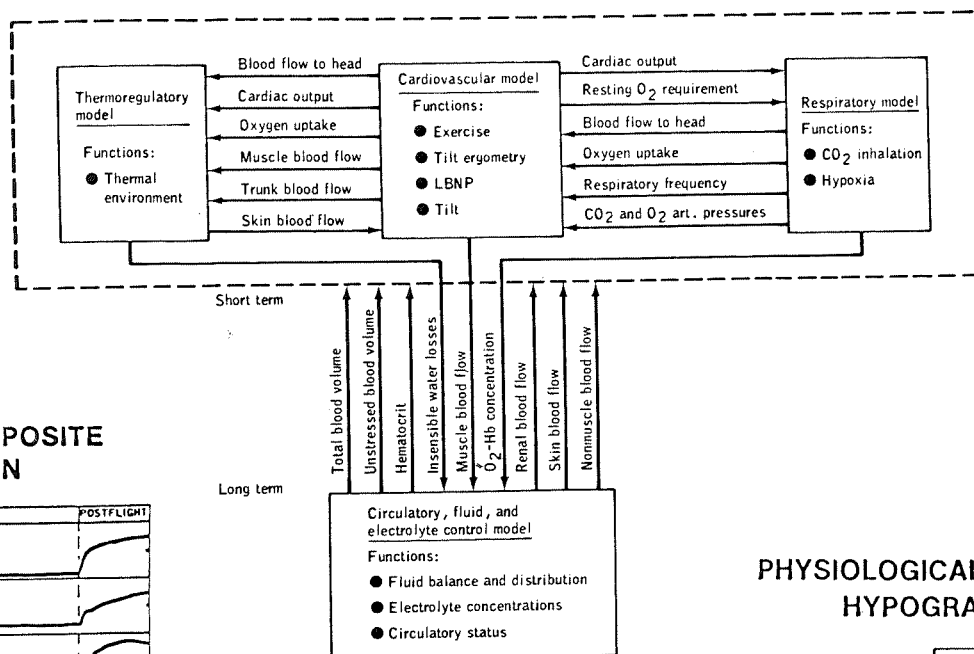
A quantitative assessment of individual susceptibility is a key in providing protection, which can take the form of selected cabin and unit pressure combinations and "pre-breathing" oxygen to remove nitrogen gas from the body. The quantitative assessment would involve an index of physiological correlates including age, sex, lean-to-fat ratio, exercise, and effectiveness of inert gas elimination.

The present task consolidates existing data on the above factors from the scientific literature and from NASA operational experience and in-house laboratory studies into a format suitable for computer analysis. New data from crewmembers will enable the comparison of a given individual with the astronaut and general populations as to the degree of protection required in space.

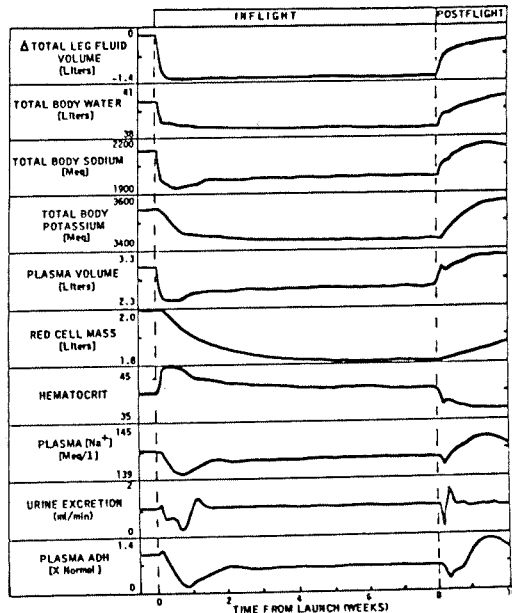
PUBLICATIONS

1. Horrigan, D. J., Jr., and Waligora, J. M. "The development of effective procedures for the protection of Space Shuttle crews against decompression sickness during extravehicular activities." Proc. Aerospace Med. Assoc. Sci. Mtg., May 1980.

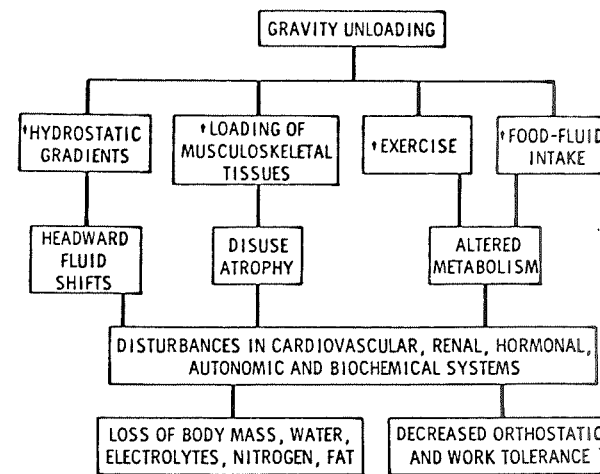
WHOLE-BODY ALGORITHM



SIMULATION OF COMPOSITE SKYLAB MISSION



PHYSIOLOGICAL EFFECTS DURING HYPOGRAVIC STUDIES



PHYSIOLOGICAL SYSTEMS ANALYSIS

R. J. White (MATSCO)

An interdisciplinary approach is taken which involves a set of mathematical models capable of simulating a number of physiological subsystems.

A major objective that was achieved is the integration of several models into a larger "whole-body algorithm." The whole-body algorithm was designed to examine many different physiological systems during a simulation of long-duration spaceflight.

Each physiological subsystem appears to have its own time course of adaptation and may be viewed as a type of control system operating with negative feedback to restore stability following a disturbance.

PUBLICATIONS

1. Kimzey, S. L., Leonard, J. I., and Johnson, P. C. "A mathematical and experimental simulation of the hematological response to weightlessness." ACTA ASTRONAUTICA 6:1289-1303, 1979.

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DIAGNOSIS OF PRE-CLINICAL VIRAL ILLNESS

J. G. Tilles (California College of Medicine, Irvine Medical Center)

Individuals who appeared perfectly healthy at launch time may exhibit symptoms of acute viral illness in flight. This problem may be resolved if pre-clinical viral illness can be diagnosed while the individual is still on Earth. A possible approach, being investigated in this research project, is to detect low levels of interferon that might be produced naturally during the incubation period.

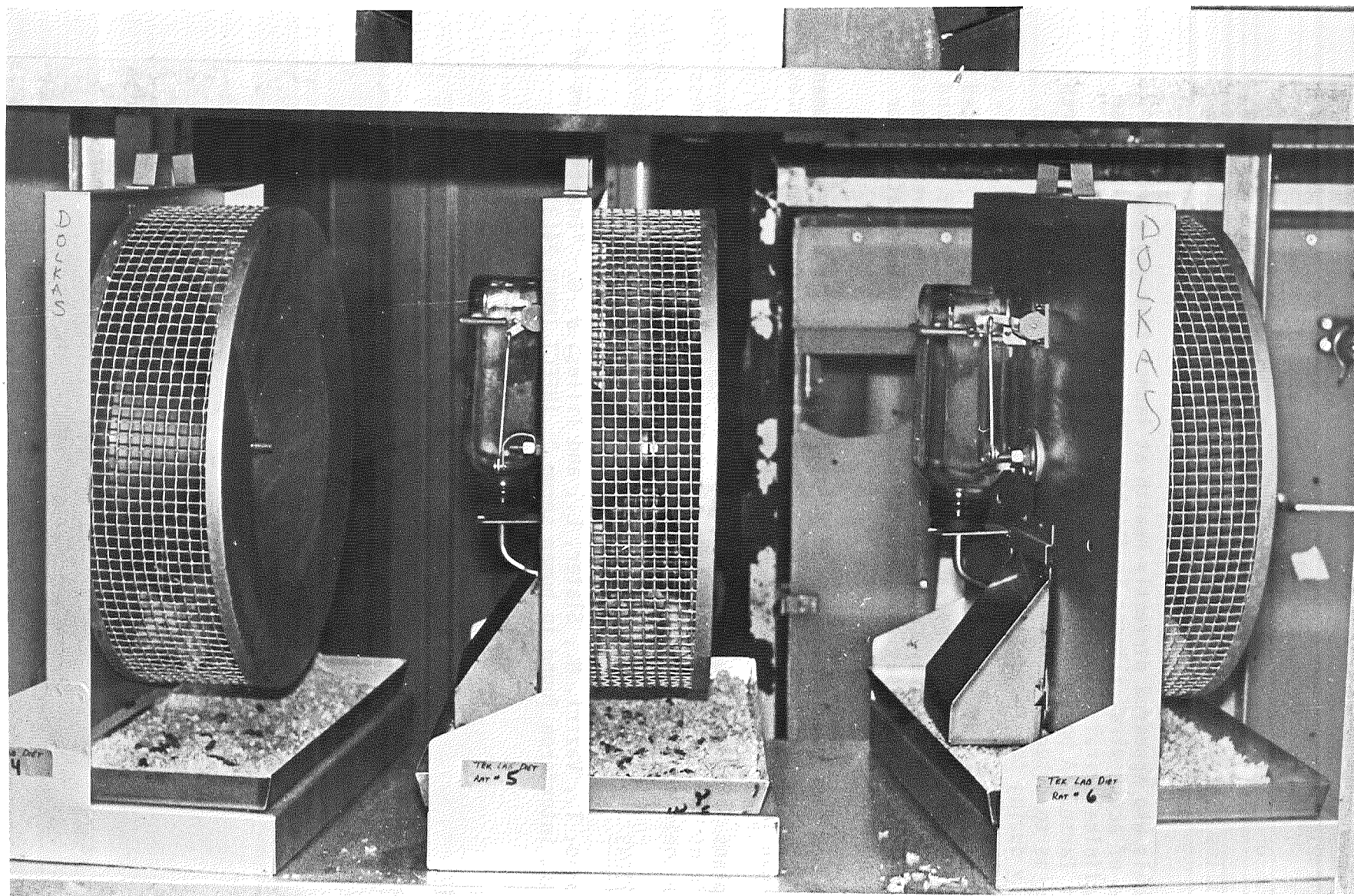
The sensitivity of the standard bioassay for interferon has been enhanced through the use of polycations, aged cells, sensitive strains of cell and virus, and control of assay conditions. In addition, a sensitive microassay and a rapid leukocyte assay have been developed. A radioimmunoassay for interferon is also being developed.

The work has been complicated by the identification of six different human interferons. Physical-chemical, immunological, and biological differences among these interferons have been documented.

Future plans include the use of the various assays to detect interferon in specimens taken from patients throughout the course of clinical illness and from their contacts before clinical symptoms develop.

PUBLICATIONS

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Three views of exercise wheel used in set-up for rats undergoing exercise/diet regimen. Note the food compartment and water bottle attached to the back of the right wheel. Note also the revolution counter near the top of the water bottle. Careful scrutiny will reveal white rats in the cages.

FACTORS REGULATING CARBOHYDRATE METABOLISM IN SIMULATED WEIGHTLESSNESS

C. B. Dolkas (Veterans Administration Hospital, Palo Alto)

Previous studies have clearly established that during prolonged bedrest the body develops a state of insulin resistance. This state is also present in a number of clinical abnormalities such as diabetes, uremia, obesity, etc.

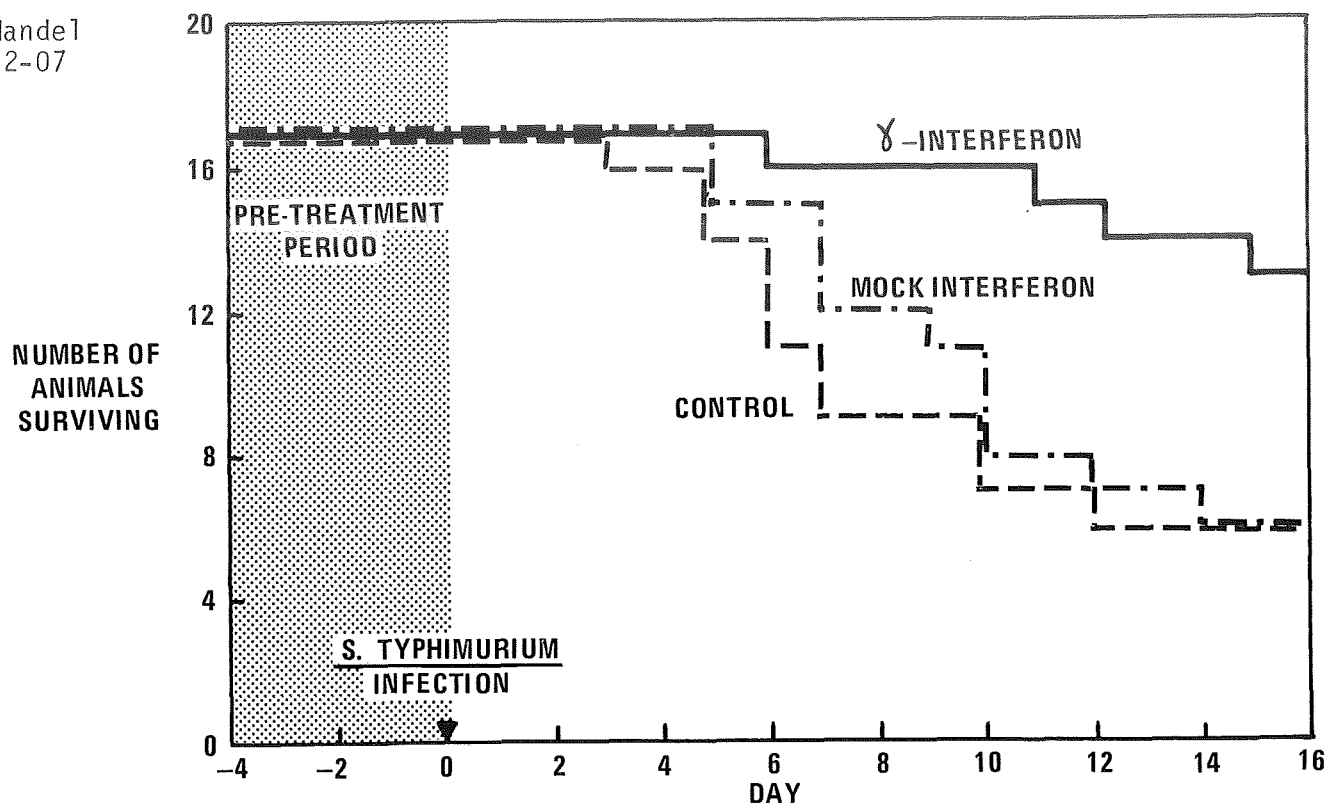
This phenomenon of insulin resistance has been duplicated in laboratory rats, where it has been shown to increase with age. It is entirely possible that with returning Space Shuttle travelers, who may be older and less conditioned than previous astronauts, the persistent insulin resistance would prevent their full recovery.

In rats, exercise training and chronic centrifugation prevents insulin resistance. Also in exercise-trained rats, the skeletal muscle (a substantial consumer of glucose) is the primary site of the enhanced insulin sensitivity, while the liver is less responsive to insulin.

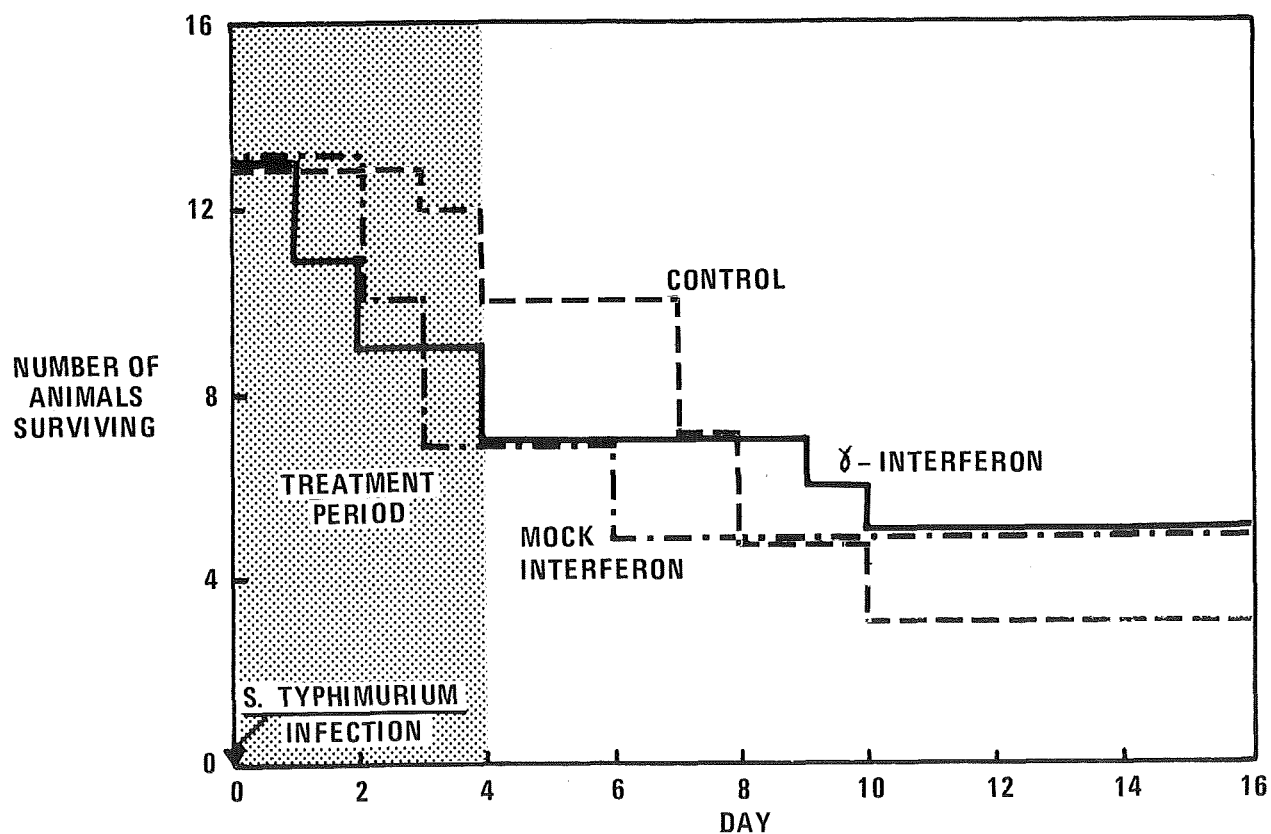
The effects of diet on these phenomena are being studied.

PUBLICATIONS

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2. Mondon, C., Economos, A., and Dolkas, C. B. "Evidence for muscle activity factor in lymph of spontaneously exercised rats." CLIN RES 28:82, 1980.
3. Mondon, C. E., Dolkas, C. B., and Reaven, G. M. "Site of enhanced insulin sensitivity in exercise trained rats at rest." AMER J PHYSIOL 239:E169, 1980.



Effect of γ -interferon on *S. typhimurium* infection. Above: Mice were pre-treated with interferon injections from day -4 for five days. The bacterium was injected on day 0. Note a significant effect of interferon on the survival of infected mice. Below: Mice were infected and began treatment on day 0. Treatment continued to day 4. Note that treatment had no significant effect on the survival of infected mice.



EARLY DISEASE SUSCEPTIBILITY WITH INTERFERON

A. D. Mandel (NASA-ARC)

Studies to date have concentrated on the role of interferon in resistance to disease. Interferon can regulate immune responses, activate natural killer cells, and modulate the expression of tissue antigens on lymphoid cells, all in a mouse model.

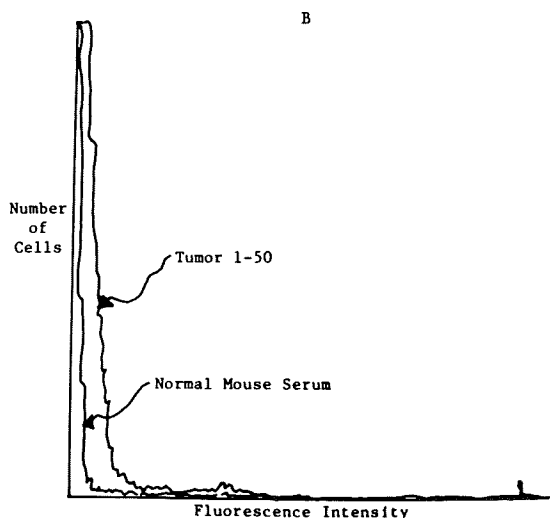
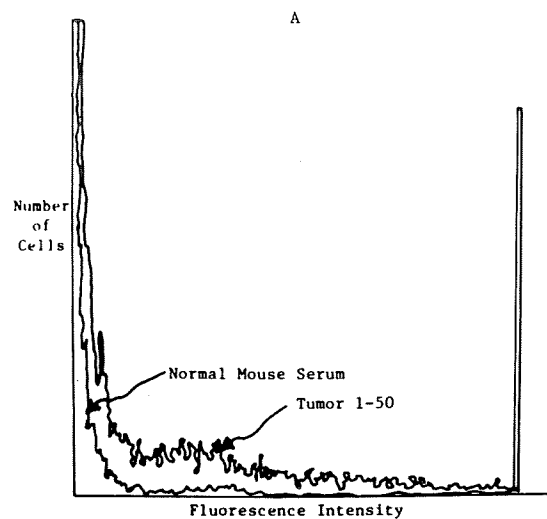
Of specific interest is Type II interferon, a new type of interferon that is produced as part of the immune response and is much more effective in these activities than is the classical Type I interferon studied elsewhere. Follow-up on these initial studies shows that pretreatment of mice with Type II interferon makes these mice more resistant to infection with the pathogen Salmonella typhimurium.

Initial studies with human interferon suggest that there may be some genetic control over an individual's response to interferon. This may eventually prove useful in selecting candidates for spaceflight. Alterations in interferon production or action may also prove useful as an indicator of infection.

Future studies will involve the effects of simulated spaceflight on interferon response of mice and rats.

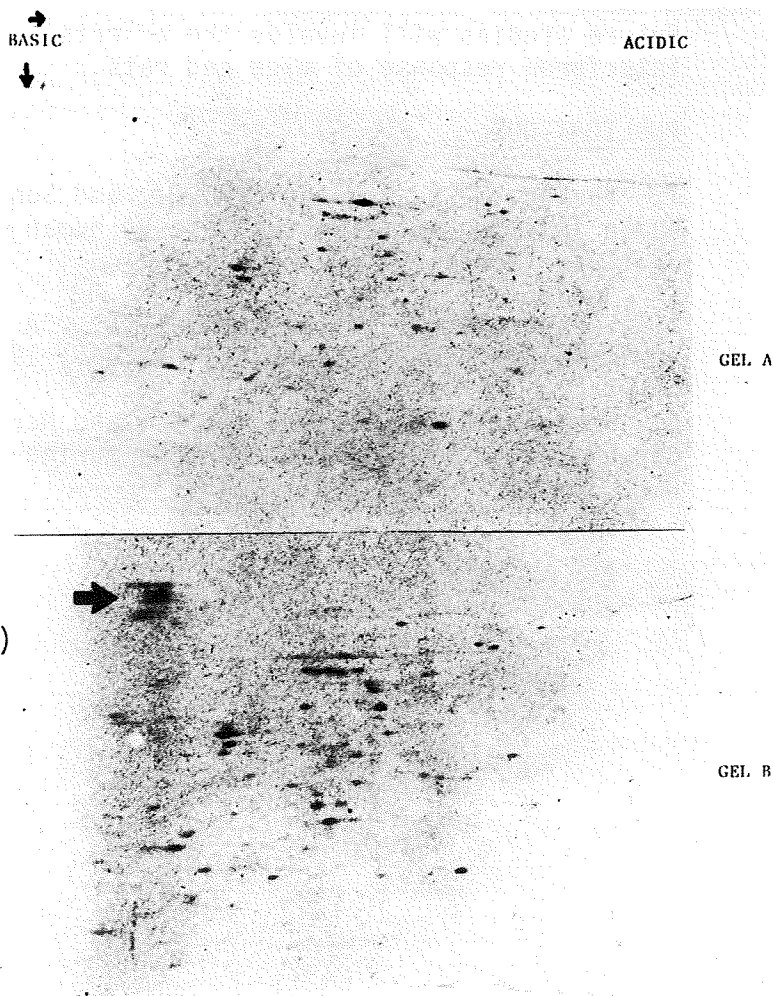
PUBLICATIONS

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2. Sonnenfeld, G. and Merigan, T. C. "A regulatory role for interferon in immunity." ANN NY ACAD SCI 332:345, 1979.
3. Sonnenfeld, G., Mandel, A. D., and Merigan, T. C. "Time and dosage dependence of immunoenhancement by murine type II interferon preparations." CELL IMMUNOL 40:285-293, 1978.



Left: Fluorescence Activated Cell Sorter (FACS) analysis of serum from mice in which the monoclonal antibody-producing hybridoma Tumor 1-50 grew as an antibody-secreting tumor. (A) Human peripheral T cells, purified by rosetting with sheep erythrocytes; normal mouse serum used as control. (B) Lack of reactivity of Tumor 1-50 against B-cell containing peripheral leukocyte population.

Right: Autoradiogram of two-dimensional gels of immunoprecipitated extracts of ^{35}S -methionine-labeled human peripheral T cells. (Gel A) Precipitated with normal mouse serum. (Gel B) Precipitated with monoclonal anti-T-cell subpopulation antibody.



STUDIES WITH B- AND T-CELL HYBRIDOMAS

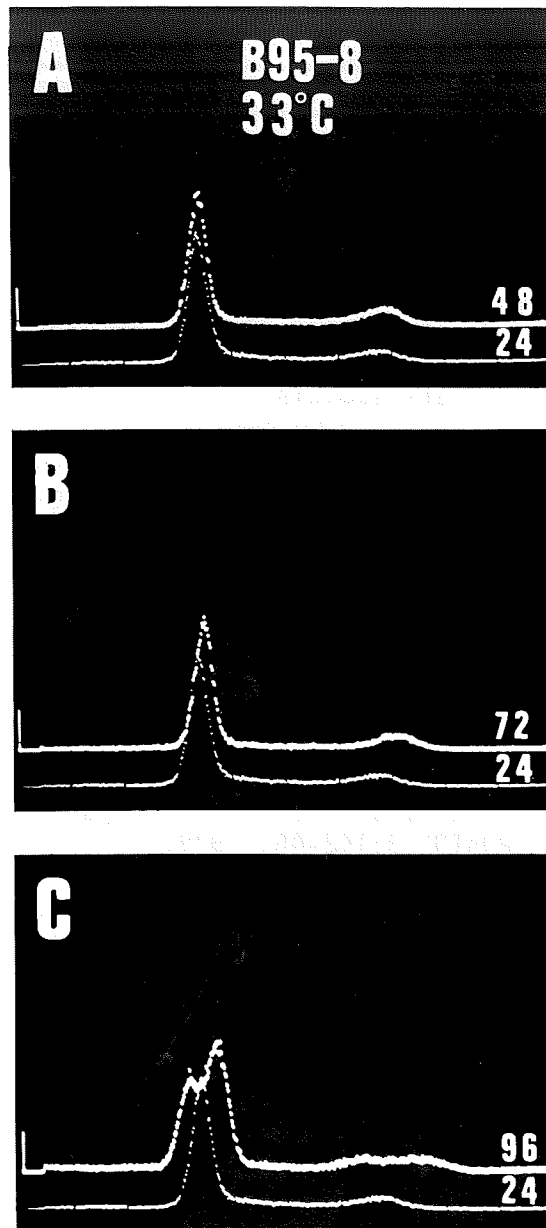
R. A. Goldsby (University of Maryland)

Surface properties of human mononuclear leukocytes are of great interest because they identify functionally different populations of cells in the immune system. One of the two major classes of lymphocytes, T cells, is made up of discrete subpopulations. Each subpopulation conducts a number of immunologic functions in cell-mediated lympholysis and humoral and cell-mediated immune responses. A major focus of this research is the construction and characterization of antibody-producing hybridomas, which secrete monoclonal antibodies for human T-cell subsets.

One such hybridoma, Tumor 1-50, interacts with T cells but not B cells. Further work has shown that this monoclonal antibody specifically recognizes a subpopulation which comprises only one-third of peripheral T cells.

PUBLICATIONS

1. Suomalainen, H. A., Goldsby, R. A., Osborne, B. A., and Schroder, J. "Mouse/human T-cell hybrids rosetting with sheep erythrocytes." SCAND J IMMUNOL 11:163-68, 1980.
2. Goldsby, R. A., Osborne, B. A., and Engleman, E. G. "Identification, isolation, and characterization of a human T-cell population by a monoclonal antibody." CURR MICROBIOL 3:142-46, 1979.
3. Goldsby, R. A., Osborne, B. A., Suri, D., Williams, J., and Mandel, A. D. "Preservation of polyclonal antibody production by hybridization." CURR MICROBIOL 2:152-62, 1979.



Flow cytofluorometric detection of Epstein-Barr viral replication. Fluorescence/cell is depicted on the horizontal axis while the corresponding number of cells demonstrating a particular fluorescent content is depicted on the vertical axis. In (A) to (C), the lower (nonhighlighted) profile is a histogram of the DNA content in a B95-8 cell population 24 hrs after a downshift in incubation-temperature from 37 to 33°C. The upper (highlighted) profile represents the DNA content 48 hrs (A), 72 hrs (B), and 96 hrs (C) after the downshift in temperature. Note the changes to greater DNA content profiles especially evident at 48 and 96 hrs after the downshift.

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AUG 1980

CYTOFLUOROMETRIC ANALYSIS OF VIRAL INFECTIONS

W. J. Meinke (University of Arizona School of Medicine)

Flow microfluorometry (FMF) permits the quantitative analysis of cell populations that have been stained with a fluorescent dye specific for a cellular component. FMF analyses have demonstrated a marked ability to detect cellular changes which may be highly diagnostic in infectious diseases.

Eucaryotic cells which were variously infected with a type of herpes simplex virus were stained with mithramycin and subsequently examined. FMF analysis detected viral replication within the lytically infected cell population; low levels of replication were also detected in persistently infected cells. FMF profiles correlated significantly with morphological observations of infected cultures.

In future studies, identical cultures of selected cell lines will be infected with ten pathologically important viral groups. At regular intervals following infection, the infected cell populations will be examined by FMF and compared with uninfected populations.

PUBLICATIONS

1. Dunn, J., Meinke, W. J., and Spizizen, J. "Further characterization of herpes virus persistence." J GEN VIROL 43:467-72, 1979.

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NUTRITIONAL CONTROL OF NEUROTRANSMITTERS

R. J. Wurtman (Massachusetts Institute of Technology)

Investigators have found that certain dietary substances affect the synthesis of neurotransmitters in autonomic and brain neurons. Food consumption may change the plasma levels of choline/lecithin, tryptophan, and tyrosine, which may in turn affect acetylcholine, norepinephrine, and serotonin.

Attention in this effort has been given to tyrosine's and tryptophan's effects on blood pressure, their effects and that of lecithin on alertness and performance in normal individuals, and to nutrient effects on transmitters associated with memory. Accomplishments include new findings on the mechanisms by which tyrosine and tryptophan lower blood pressure in hypertensive rats and the observation that tyrosine relieves depression and Parkinson's disease in humans. Another interesting discovery is that whereas carbohydrate ingestion stimulates serotonin synthesis in the brain of normal rats, it does not do so in diabetic rats.

Future work will explore further the ability of tryosine and tryptophan to lower blood pressure in hypertensive humans and the mechanisms of this effect in rats. The use of tyrosine to treat Parkinson's disease and depression and the ability of choline/lecithin to improve memory will also be investigated.

PUBLICATIONS

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2. Gelenberg, A. J., Wojcik, J. D., Growdon, J. H., Sved, A. F., and Wurtman, R. J. "Tyrosine for the treatment of depression." AM J PSYCHIAT 137:622, 1980.

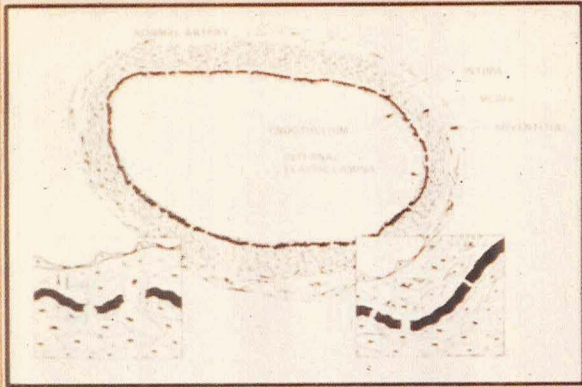
COMPUTER DIAGNOSIS OF ATHEROSCLEROSIS - PROBLEM

Selzer
94-01

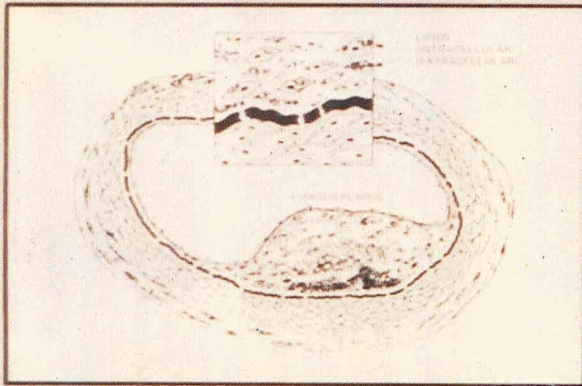
APPEARANCE OF ATHEROSCLEROSIS

(ARTERIAL NARROWING FROM FATTY
AND FIBROUS PLAQUE DEPOSITS)

DRAWING OF NORMAL ARTERY

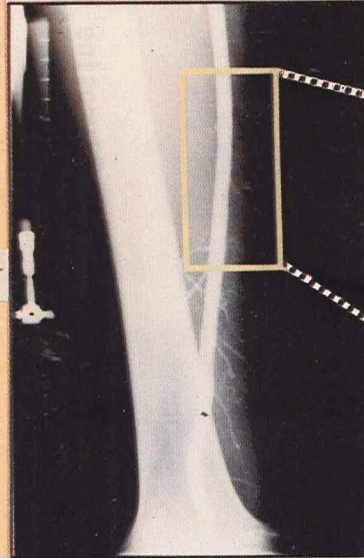


DRAWING OF DISEASED ARTERY SHOWING FIBROUS PLAQUE

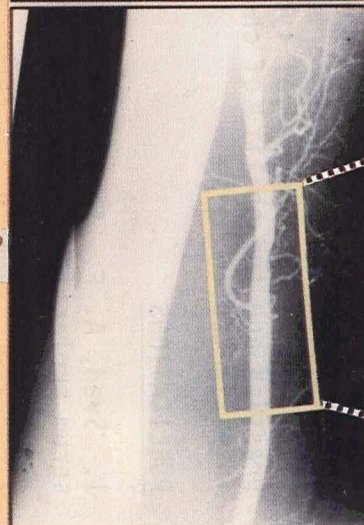


FEMORAL X-RAY ANGIOGRAMS

MINIMAL
DISEASE



ADVANCED
DISEASE



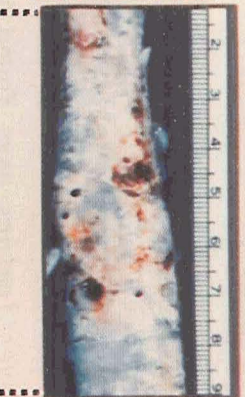
POST-MORTEM
CASTS OF
SECTION
OF FEMORAL
ARTERY SHOWN
IN ANGIOGRAM



EXTRACTED
ARTERY CUT
LENGTHWISE AND
OPENED. VESSEL
IS NEAR-NORMAL



EXTRACTED ADVANCED
DISEASE ARTERY
SHOWING ULCERATION
CALCIFICATION AND
HEMORRHAGE



ADVANCED RESEARCH IN BIOMEDICAL IMAGE PROCESSING

R. H. Selzer (JPL-CIT)

The ultimate goal of this research is to develop methods to detect and assess latent cardiovascular disease. The project involves inducing arterial disease in animals and measuring pressure and flow in the diseased arteries. Bench flow tests with simulated vessels made from arterial casts are also conducted, with computer modeling and simulation of the flow. Arterial flow resistance may be a major factor in the assessment of cardiac risk for individuals with early arterial disease who are subjected to high stress.

Another research effort uses automated light microscope imaging techniques to analyze muscle and bone changes associated with zero gravity. In results from muscle fibers from rats flown on Cosmos 1129, the slow fibers showed more spaceflight-induced size loss than fast fibers. The proportion of slow fibers was also lower in the flight groups, suggesting spaceflight-induced fiber type conversion from slow to fast.

PUBLICATIONS

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2. Selzer, R. H., Crawford, D. W., Brooks, S. H., and Blankenhorn, D. H. "Synthesis of carotid arteriograms by intravenous contrast delivery and multiframe computer averaging." CIRCULATION 60(4):12, 1979.
3. Blankenhorn, D. H., Brooks, S. H., Selzer, R. H., and Barndt, R. "Rate of atherosclerosis change during treatment of hyperlipoproteinemia." CIRCULATION 57(2):355-61, 1979.

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AN IMPROVED MEDICAL ULTRASOUND IMAGING SYSTEM

J. D. Hestenes (JPL-CIT)

The objective of this task is to develop methods for the extraction and analysis of physiological features from ultrasound images using dog arterial and cardiac systems. Under examination are radial motion, contraction, wall bending, and boundary delineations which are required for physiological description.

Improvements in image resolution and extraction of physiological features have been made. A real-time video buffer system successfully produces mosaic images of the heart at selected times of the cardiac cycle. A data acquisition system allows for the on-site control of the quality of ultrasound images recorded on video. The implementation of video discs eliminates 90 mm film media and permits direct video methods. Real-time software development is continuing.

PUBLICATIONS

None

